Journal of
THE CHEMICAL SOCIETY

Committee of Publication

Chairman: Sir Cyril Hinshelwood, M.A., Sc.D., F.R.S.

Sir Wallace Akers, C.B.E., D.C.L., D.Sc., F.R.S.
J. S. Anderson, M.Sc., Ph.D., F.R.S.
D. H. R. Barton, Ph.D., D.Sc., F.R.I.C.
C. E. H. Bawn, B.Sc., Ph.D., F.R.S.
D. J. Bell, Sc.D., Ph.D.
R. P. Bell, M.A., B.Sc., F.R.S.
E. J. Bowen, M.A., D.Sc., F.R.S.
H. Burton, Ph.D., D.Sc., F.R.I.C.
A. H. Cook, D.Sc., F.R.I.C., F.R.S.
C. A. Coulson, M.A., D.Sc., F.R.S.
F. S. Dainton, M.A., Ph.D.
C. W. Davies, D.Sc., F.R.I.C.
H. J. Emeléus, D.Sc., A.R.C.S., F.R.S.
F. Fairbrother, D.Sc.
R. D. Haworth, D.Sc., Ph.D., F.R.S.
E. D. Hughes, D.Sc., F.R.I.C., F.R.S.
H. R. Ing, M.A., D.Phil., F.R.S.
C. K. Ingold, D.Sc., F.R.I.C., F.R.S.
H. M. N. H. Irving, M.A., D.Phil., F.R.I.C.
F. G. Mann, Sc.D., F.R.I.C., F.R.S.
R. A. Morton, D.Sc., Ph.D., F.R.S.
L. N. Owen, Ph.D., D.Sc., F.R.I.C.
J. M. Robertson, M.A., D.Sc., F.R.S.
H. N. Rydon, D.Sc., D.Phil., F.R.I.C.
N. Sheppard, M.A., Ph.D.
C. W. Shoppee, D.Sc., D.Phil., F.R.I.C.
W. F. Short, D.Sc., M.Sc.
R. Spence, C.B., Ph.D., D.Sc., F.R.I.C.
M. Stacey, Ph.D., D.Sc., F.R.S.
L. E. Sutton, M.A., D.Phil., F.R.S.
J. Walker, Ph.D., D.Phil., D.Sc.
W. A. Waters, M.A., Sc.D., F.R.I.C.
T. S. Wheeler, Ph.D., D.Sc., F.R.I.C.

Editor

R. S. Cahn, M.A., D.Phil.Nat., F.R.I.C.

Assistant Editors

A. D. Mitchell, D.Sc., F.R.I.C.
L. C. Cross, Ph.D., A.R.C.S., F.R.I.C.
A. E. Somerfield, B.A., B.Sc.

NOVEMBER, 1953

Subscription rate to non-Fellows £10 0s. 0d. per annum post free

LONDON: THE CHEMICAL SOCIETY, BURLINGTON HOUSE, W.1.

THE CHEMICAL SOCIETY

PATRON

HER MAJESTY THE QUEEN

President

C. K. Ingold, D.Sc., F.R.I.C., F.R.S.

Vice-Presidents

who have filled the office of President

F. G. Donnan, C.B.E., D.Sc., LL.D., F.R.S.
Sir Ian Heilbron, D.S.O., D.Sc., LL.D., F.R.S.
Sir Cyril Hinshelwood, M.A., Sc.D., F.R.S.
W. H. Mills, M.A., Sc.D., F.R.S.
Sir Eric Rideal, M.B.E., M.A., D.Sc., F.R.S.
Sir Robert Robinson, O.M., D.Sc., LL.D., F.R.S.

Vice-Presidents

G. R. Clemo, D.Phil., D.Sc., F.R.S.
R. D. Haworth, D.Sc., Ph.D., F.R.S.
D. H. Hey, Ph.D., D.Sc., F.R.I.C.
E. L. Hirst, D.Sc., LL.D., F.R.S.
Sir John Simonsen, D.Sc., F.R.I.C., F.R.S.
M. Stacey, Ph.D., D.Sc., F.R.S.

Treasurer

Sir Wallace Akers, C.B.E., D.C.L., D.Sc., F.R.S.

Secretaries

H. Burton, Ph.D., D.Sc., F.R.I.C.
E. D. Hughes, D.Sc., F.R.I.C., F.R.S.
L. E. Sutton, M.A., D.Phil., F.R.S.

Ordinary Members of Council

G. Baddeley, M.Sc., Ph.D., D.Sc.
Wilson Baker, M.A., D.Sc., F.R.S.
D. H. R. Barton, Ph.D., D.Sc., F.R.I.C.
J. Bell, D.Sc., Ph.D., F.R.I.C.
R. P. Bell, M.A., B.Sc., F.R.S.
F. Bergel, D.Phil.Nat., D.Sc., F.R.I.C.
Neil Campbell, D.Sc., Ph.D.
J. Chatt, M.A., Ph.D., F.R.I.C.
M. J. S. Dewar, M.A., D.Phil.
I. J. Faulkner, B.Sc., Ph.D., F.R.I.C.
S. J. Gregg, Ph.D., A.R.C.S., F.R.I.C.
Brynmor Jones, Sc.D., Ph.D., F.R.I.C.
F. B. Kipping, M.A., Ph.D.
E. A. Moelwyn-Hughes, D.Phil., D.Sc., Sc.D.
H. M. Powell, M.A., B.Sc., F.R.S.
A. Robertson, M.A., Ph.D., F.R.S.
M. A. T. Rogers, B.Sc., Ph.D., A.R.I.C.
C. W. Shoppee, D.Sc., D.Phil., F.R.I.C.
J. W. Smith, Ph.D., D.Sc., F.R.I.C.
T. S. Stevens, B.Sc., D.Phil., A.R.I.C.
A. R. J. P. Ubbelohde, M.A., D.Sc., F.R.S.
A. I. Vogel, D.Sc., D.I.C., F.R.I.C.

Ex-Officio Members of Council

A. Findlay, C.B.E., D.Sc., LL.D., F.R.I.C. (*Chairman of the Chemical Council*)
W. Wardlaw, C.B.E., D.Sc., F.R.I.C. (*Chairman of the Joint Library Committee*)

General Secretary

J. R. Ruck Keene, M.B.E., T.D., B.A.

Librarian

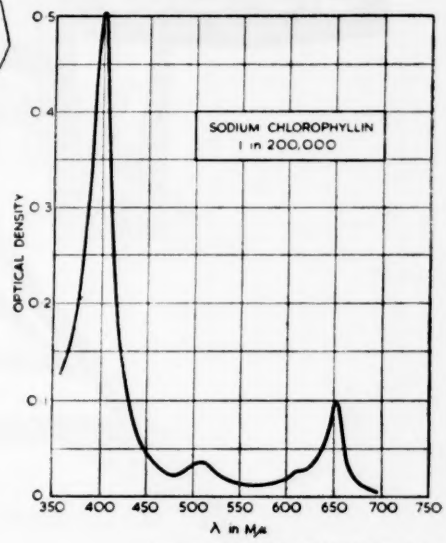
A. E. Cummins

Telephone Numbers: Regent 0675/6

UNICAM

SP.600 (3,600—10,000 Å)

SPECTROPHOTOMETER



by courtesy of the Allen Chlorophyll Co. Ltd.

HIGH RESOLUTION

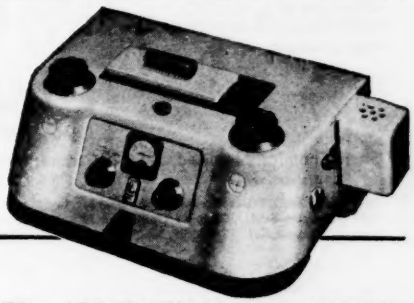
SIMPLICITY

MODERATE PRICE

FOR PHARMACOLOGY

In the manufacture of drugs and medicines, where purity is essential, rapid, precise and complete details of analysis are equally important to the research worker and the chemist in charge of production. The SP.600 Spectrophotometer allows methods developed in the laboratory to be applied in the factory with the same ease, accuracy and economy. The graph above illustrates the performance of the instrument which is equipped with a glass prism monochromator and two vacuum photocells, and may be operated from suitably stabilised mains or a 12v battery.

An illustrated leaflet describing the instrument in detail will gladly be sent on request.



EARLY DELIVERY

UNICAM INSTRUMENTS (CAMBRIDGE) LTD · ARBURY WORKS · CAMBRIDGE

U130C

These new Shell products have many important applications in Industry. For example: as SOLVENTS in the manufacture of lacquers, plastics, leathercloth and polishes; as CLEANING AND DEHYDRATING AGENTS in the photographic printing and electroplating trades.

I.P.S.1 specification

PURITY: 99% Isopropyl Alcohol by weight.
SPECIFIC GRAVITY at 20°/20°C: 0.785-0.790.
COLOUR: Water White.
DISTILLATION RANGE (A.S.T.M. D268): Minimum 95%, 81-83°C.
NON-VOLATILE MATTER: Maximum 0.01% weight.

I.P.S.2 specification

PURITY: Minimum 85% Isopropyl Alcohol by weight.
SPECIFIC GRAVITY: at 20°/20°C: 0.815-0.820
COLOUR: Water White.
DISTILLATION RANGE (A.S.T.M. D268): Minimum 95%, 78-81°C.
NON-VOLATILE MATTER: Maximum 0.01% weight.

SHELL

Shell Chemicals Limited, 105-109 Strand, London, W.C.2. Tel: Temple Bar 4455
(DISTRIBUTORS)

Divisional Offices: Walter House, Bedford Street, London, W.C.2. *Tel:* Temple Bar 4455. 42 Deansgate, Manchester, 3. *Tel:* Deansgate 6451. Clarence Chambers, 39 Corporation Street, Birmingham 2. *Tel:* Midland 6954. 28 St. Enoch Square, Glasgow, C.1. *Tel:* Glasgow Central 9561. 53 Middle Abbey Street, Dublin. *Tel:* Dublin 45775. A3

Important chemical news!

HYDRAZINE

FOR INDUSTRY

IS NOW AVAILABLE TO ALL

and Whiffens can give immediate delivery of Hydrazine compounds produced by Genatosan Ltd.

FOR ENGINEERING—for boiler water de-oxygenation

FOR PLASTICS—for new plastics and resins

FOR MEDICINE—in anti-tubercular drugs

FOR RUBBER—as blowing agents

FOR AGRICULTURE—in plant growth inhibitors

Samples, prices and full technical information available on request.
CONSULT WHIFFENS FIRST ON YOUR PROBLEMS

WHIFFENS

fine chemicals for industry

WHIFFEN & SONS LTD., NORTH WEST HOUSE, MARYLEBONE ROAD, LONDON, N.W.1
Telephone: PADdington 1041/6 *Telegrams: Whiffen, Norwest, London*

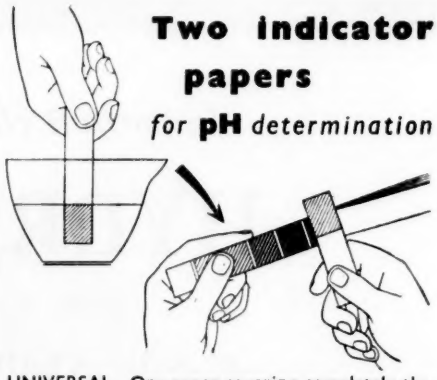
L. LIGHT & Co Ltd

"New Items—not in 1953 Catalogue"

Podophyllotoxine	54/- G
Polyvinyl alcohol (viscosity of 4% aqueous soln. 7 cps.)	34/- K
***allo*Pregnanediol**	120/- G
***n*-Propyl mercaptan** (500 gr. amps.)	22/- H
***iso*-Propyl mercaptan** (500 gr. amps.)	22/- H
Propyl-*p*-hydroxy benzoate	15/- H
***iso*-Propyl nitrate**	28/- K
Protease	9/- D
Pteroyl-triglutamic acid (20 mg. amps.)	30/- amp.
Pyridine-4-aldehyde-hydrate	62/- H
Pyridine-3-sulphonic acid	12/- D
Pyridoxal hydrochloride	136/- G
Pyridyl-2-carbinol	11/- D
Pyridyl-3-carbinol	27/- D
Pyridyl-4-carbinol	13/- D
2-Pyridyl hydroxy methyl sulphonic acid	36/- H
3-Pyridyl hydroxy methyl sulphonic acid	12/- D
4-Pyridyl hydroxy methyl sulphonic acid	31/- H
Quinhydrone	15/- H
Resazurin tablets for milk test (in bottles of 100)	10/-
Sarsasapogenin	25/- G
Silicon-oxyhydride	30/- H
Sodium methoxide (sodium methylate)	48/- K
Sodium taurocholate	29/- H
Spermidine phosphate	34/- G
Succinamide	34/- H
Succinyl sulphathiazole	54/- H
Sulphamic acid	35/- K
β-1 : 2 : 3 : 4-Tetra-*O*-acetyl-6-*O*-triphenylmethyl glucose	10/- G
3 : 3' : 4 : 4'-Tetra-amino-diphenyl HCl (3 : 3-diamino-benzidine HCl)	20/- G
Tetra-*n*-butyl titanate	76/- K
Tetraethyl-ethylene diamine	32/- H
Tetraglycine hydroperiodide	52/- H
Tetra-hydro-2-methyl-quinoline	67/- H
Tetra-iodo-thiophene	25/- D
Thiolactic acid	45/- H
Thionine (Lauth's violet)	12/- D
Thiothymine	80/- D
Thiourea dioxide (formamidine sulphinic acid)	63/- K
Thorium nitrate (pure)	14/- H
Thymol phthalein	9/- D
2 : 4 : 5-Triamino-6-hydroxy-pyrimidine di-HCl	97/- D
4 : 5 : 6-Triamino-pyrimidine	60/- G
Trichloro-acetonitrile	33/- H
2 : 4 : 6-Trichlorophenol (m. p. 64/65° C.)	33/- K
Tri-*n*-decylamine	190/- H
Tri-*n*-decylic acid	6/- G
Triethylene melamine (TEM)	15/- D
Triglycollamic acid (m. p. 246—9° C.)	27/- H
Trigonellin	18/- G
2 : 4 : 6-Triphenyl-*s*-triazine	41/- D
Trypsin lyophiled ex beef pancreas (5–8 northrup units per mg.)	59/- G
D-Tryptophane	35/- G
Tyrothricine	12/- G
Uramil (5-amino-barbituric acid)	18/- D
n-Valeric anhydride	55/- H
Vitamin B_{12} (100 mg. amps.)	320/- amp.
Xanthopterin (2-amino-4 : 6 dihydroxy-pteridine)	120/- G
β-L-Xylose	16/- G

POYLE TRADING ESTATE

COLNBROOK BUCKS ENGLAND



Two indicator papers

for **pH** *determination*

UNIVERSAL One paper covering completely the range from 1 to 10 enabling pH values to be checked to within 0.5 pH.

COMPARATOR Four separate books for work requiring greater accuracy. With these papers the pH value of any solution can be ascertained to within 0.3 pH.

Descriptive leaflet will be sent free on request.

JOHNSONS OF HENDON LTD

London, N.W.4

Est. 1743

DICYANDIAMIDE

now available

for immediate delivery

from

CHEMICALS DIVISION

THE BRITISH OXYGEN CO. LTD.

Vigo Lane, Chester-le-Street, Co. Durham

Telephone: Birtley 145

AT REIGATE [redacted]

OUR JOB

AS ESSENCE MANUFACTURERS

IS TO TAKE NATURAL PRODUCTS WHICH HAVE A FLAVOUR OR AROMA OR BOTH; EXTRACT FROM THEM THE PRINCIPLES RESPONSIBLE FOR THAT FLAVOUR AND AROMA, AND THEN PREPARE THESE PRINCIPLES IN SUCH A FORM AS TO BE EASILY AND CONVENIENTLY AND ECONOMICALLY USED BY OUR CUSTOMERS.

WE ARE SPECIALISTS IN THIS FIELD AND CAN OFFER GUARANTEED NATURAL PRODUCTS WHICH FOR QUALITY AND TRUE FLAVOUR ARE IN A CLASS BY THEMSELVES.

REIGATE BRAND—

VANILLA NATURA
GRAPEFRUIT NATURA
ORANGE NATURA
(SWEET OR BITTER)
ORRIS NATURA

WHITE, TOMKINS & COURAGE, LTD.
NORTH ALBERT WORKS, REIGATE

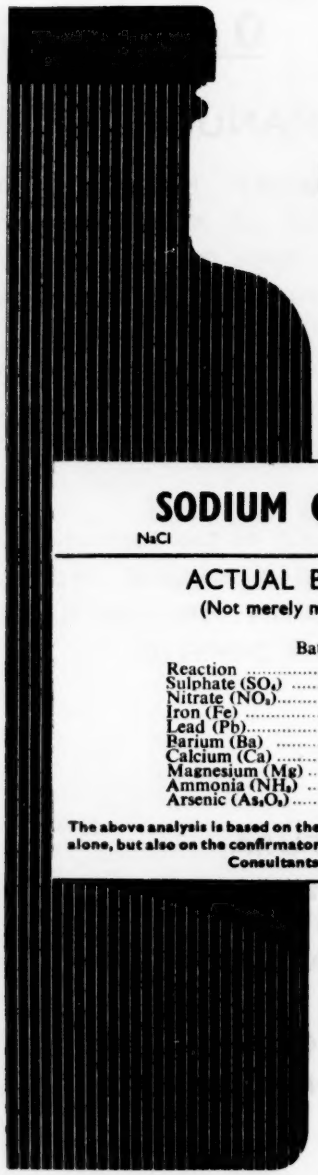
TELEGRAMS: ESSWHITE, REIGATE TELEPHONE: REIGATE 2242-3

ESTABLISHED 1841

the outstanding purities of

Judactan

analytical reagents



We invite you to compare the actual batch analysis shown here, with the purities guaranteed by the specifications to which you normally work — we are sure the comparison will be helpful to you.

SODIUM CHLORIDE A.R.

NaCl Mol. Wt. 58·454

ACTUAL BATCH ANALYSIS

(Not merely maximum impurity values)

Batch No. 21386

Reaction	pH 7·9
Sulphate (SO_4)	0·0002%
Nitrate (NO_3)	0·0006%
Iron (Fe)	0·00004%
Lead (Pb)	0·0001%
Barium (Ba)	0·0002%
Calcium (Ca)	0·0005%
Magnesium (Mg)	0·0005%
Ammonia (NH_3)	0·00001%
Arsenic (As_2O_3)	0·00009%

The above analysis is based on the results, not of our own Control Laboratories alone, but also on the confirmatory Analytical Certificate issued by Independent Consultants of international repute

This is the analysis of a Judactan reagent. And, as with every other reagent in the series it is the *actual batch analysis* — it is one of several of which we are especially proud.

The General Chemical & Pharmaceutical Co. Ltd., Chemical Manufacturers, Judex Works, Sudbury, Middx.

CONTENTS.

PAPERS COMMUNICATED TO THE CHEMICAL SOCIETY.

General, Physical, and Inorganic.

PAGE

677. The Thermochemistry of Organo-boron Compounds. Part II. Tri-*n*-butylboron, and the Di-*n*-butylboron Halides.
By H. A. SKINNER and T. F. S. TEES 3378

680. Methods for Computing Successive Stability Constants from Experimental Formation Curves.
By H. IRVING and (MRS.) H. S. ROSSOTTI 3397

682. The Reactions of Hexachlorodisilane with Ammonium Halides and Trimethylamine Hydrohalides.
By C. J. WILKINS 3409

684. Steric Hindrance in Analytical Chemistry. Part II. The Interaction of Ferrous Salts with 2-Substituted 1 : 10-Phenanthrolines.
By H. IRVING, M. J. CABELL, and D. H. MELLOR 3417

690. Rates of Ionization of ·O–H and :N–H Bonds.
By R. P. BELL and R. G. PEARSON 3443

691. Hydrazine. Part VI. Salts of Dimethyl Ketazine and Certain Hydrazones. The Halogeno-antimonites and -bismuthites. (With Notes on the Optical Properties of the Crystals. By H. C. G. VINCENT.)
By W. PUGH 3445

704. The Anodic Oxidation of Metals at Very Low Current Density. Part II. Nickel.
By S. E. S. EL WAKKAD and (MISS) SAYEDA H. EMARA 3504

705. The Anodic Oxidation of Metals at Very Low Current Density. Part III. Copper.
By S. E. S. EL WAKKAD and (MISS) SAYEDA H. EMARA 3508

727. Some Properties of Selenium Tetrafluoride.
By R. D. PEACOCK 3617

739. Adaptation of *Bact. lactis aerogenes* to resist Phenol and Various Alkylphenols.
By L. S. PHILLIPS and SIR CYRIL HINSHELWOOD 3679

741. Determination of Electrokinetic Charge and Potential by the Sedimentation Method. Part VI. Carborundum in Aqueous Solutions of Some Uni-univalent Electrolytes.
By G. A. H. ELTON and J. W. MITCHELL. 3690

NOTES:

748. Attempted Preparation of Cyanogen Fluoride.
By H. J. CALLOMON, H. W. THOMPSON, F. ALLAN ANDERSEN, and BÖRGE BAK . 3709

753. Bond Type in Trisacetylacetonecobalt(III).
By RICHARD O. WHIPPLE, ROBERT WEST, and KENNETH EMERSON . . . 3715

Physical Organic.

673. The Mechanism of Hydrolysis of Acid Chlorides. Part V. The Effect of Solvent and Hydroxyl Ions on the Rate of Solvolysis of Substituted Benzoyl Chlorides.
By D. A. BROWN and R. F. HUDSON 3352

678. The Kinetics of the Reduction by Titanous Chloride of Nitrobenzene and its Substitution Products.
By S. A. NEWTON, JUN., F. J. STUBBS, and SIR CYRIL HINSHELWOOD. . . 3384

679. Nucleophilic Displacement Reactions in Aromatic Systems. Part II. Kinetics of the Reactions of Chloronitropyridines and Chloro-2 : 4-dinitrobenzene with 3- and 4-Picoline.
By E. A. S. CAVELL and N. B. CHAPMAN. 3392

685. The Rearrangement of Some Dibromopropyl Esters.
By W. G. H. EDWARDS and R. HODGES 3427

687. A Comparison of the Apparent Dipole Moments of the Brominated Methanes dissolved in Benzene with the True Values determined as Gases.
By A. D. BUCKINGHAM and R. J. W. LE FÈVRE 3432

PAGE

694. The Catalytic Deuteration of Organic Compounds. Part III. Exchange Reactions of Saturated Aliphatic Carboxylic Acids.
By J. Bell, T. Hill, K. A. Macdonald, R. I. Reed, and (in part) A. Macdonald 3456

695. The Catalytic Deuteration of Organic Compounds. Part IV. The Deuteration of Optically Active Lactic Acid.
By J. Bell, K. A. Macdonald, and R. I. Reed 3459

700. The Photomutarotation of (—)-2-Chloro-2-nitrosocamphane.
By A. J. N. Hope and Stotherd Mitchell 3483

718. Studies of *N*-Halogeno-compounds. Part V. The Interaction of Dialkylchloramines with Phenols.
By L. O. Brown and F. G. Soper 3576

Notes :

751. Infra-red Absorptions of the *iso*Cyanate Group.
By W. H. T. Davison 3712

752. The Interaction of Iodine Bromide and Phenol or Aniline.
By A. G. Sharpe 3713

Organic.

670. Alkaloids of *Glycosmis arborea*. Part I. Isolation of Arborine and Arborinine : The Structure of Arborine.
By (Mrs.) D. Chakravarti, R. N. Chakravarti, and S. C. Chakravarti . . 3337

671. Nitramines and Nitramides. Part V. Nitrations of Urethane, *N*-Methylurethane, Urea, and Hexahydro-1 : 3-dinitro-1 : 3 : 5-triazine in Sulphuric Acid.
By C. Holstead, Alex. H. Lamberton, and (in part) P. A. H. Wyatt . . 3341

672. Nitramines and Nitramides. Part VI. Some *N*-Nitrations in Solvents other than Sulphuric Acid.
By C. Holstead and Alex. H. Lamberton 3349

674. Urea and Related Compounds. Part III. Alternative Syntheses of Sulphenylureas.
By Frederick Kurzer 3360

675. The Isomerisation of *iso*Flavones.
By W. B. Whalley 3366

676. Fluoro-olefins. Part II. Synthesis and Reactions of Some 3 : 3 : 3-Trihalogenopropenes.
By R. N. Haszeldine 3371

681. Some Photochemical Reactions between Quinones and Hydrocarbons.
By R. F. Moore and William A. Waters 3405

683. Homolytic Aromatic Substitution. Part IV. Partial Rate Factors for the Phenylation of Fluorobenzene, Bromobenzene, and Iodobenzene.
By D. R. Augood, J. I. G. Cadogan, D. H. Hey, and Gareth H. Williams . 3412

686. The Oxidative Hydrolysis of 4-α-Cyanobenzyl*meso*benzanthrone.
By Neil Campbell and Anthony A. Woodham 3429

688. The Course of the Perkin Coumarin Synthesis. Part I.
By Malcolm Crawford and J. A. M. Shaw 3435

689. Indoles. Part IV. Synthetical Applications of the Oxidative Fission of the $C_{(2)}$–$C_{(3)}$ Bond in Indoles.
By D. W. Ockenden and K. Schofield. 3440

692. The Scope and Mechanism of Carbohydrate Osotriazole Formation. Part I. The Action of Copper Sulphate on Glucose Methylphenylosazone and Glucose 2-*N'*-Methyl-1-*N'* : 2-*N'*-diphenylosazone.
By H. El Khadem 3452

693. The Synthesis of Homoferreirin.
By K. G. Neill 3454

696. *iso*Oxazolones. Part IV. The Bromination of Arylaminomethylene*iso*oxazolidones. A New Selective Anion-precipitant.
By G. Shaw 3464

697. *iso*Oxazolones. Part V. Arylaminoalkyl(or aryl)idene*iso*oxazolones and -*iso*-oxazolidones.
By E. Mansberg and G. Shaw 3467

698. The Structure of the Glycerinositophosphatide of Ground-nut.
By T. Malkin and A. G. Poole 3470

PAGE

699. Organic Fluoro-compounds. Part VII. Some 2-Trihalogenocoumarones.
By W. B. WHALLEY 3479

701. Friedel–Crafts Acetylation of Chrysene.
By W. CARRUTHERS 3486

702. 1 : 2-Dicarboxylic Acids. Part I. Positional Isomerides Derived from Methylsuccinic Acid; with a Note on the Rearrangement of Unsymmetrical Compounds of this Type.
By J. E. H. HANCOCK and R. P. LINSTEAD 3490

703. The Direct Formation of *cyclo*Pentanones by the Action of Mineral Acids on Carboxy-adipic Acids and Related Compounds.
By L. CROMBIE, J. E. H. HANCOCK, and R. P. LINSTEAD. 3496

706. *p*-Menthane-2 : 3-diols. Part II. Catalytic Hydrogenation of Diosphenol and Reduction by Sodium and Ethanol.
By A. KILLEN MACBETH and W. G. P. ROBERTSON 3512

707. The Preparation of Enol Ethers from Certain β-Keto-nitriles.
By B. H. CHASE and JAMES WALKER 3518

708. Melanin and Its Precursors. Part VII. Synthesis of Methylated 5 : 6-Dihydroxyindoles, β-(4 : 5-Dihydroxy-2-methylphenyl)alanine, and Related Amines.
By R. I. T. CROMARTIE and JOHN HARLEY-MASON 3525

709. Properties and Reactions of Free Alkyl Radicals in Solution. Part VI. Reactions with *N*-Halogenoanilides.
By M. C. FORD, L. J. HUNT, and WILLIAM A. WATERS 3529

710. Wool Wax. Part IV. The Constitution of the Aliphatic Diols.
By D. H. S. HORN and F. W. HOUGEN 3533

711. Studies with Dithizone. Part V. A Comparison of Routes for the Synthesis of [^{35}S]Dithizones.
By H. IRVING and C. F. BELL 3538

712. The Structures of Some Monoquaternary Salts of 5-Substituted 4 : 7-Phenanthrolines.
By W. O. SYKES 3543

713. Synthesis of 2 : 6-Diamino-3-arylpyridines.
By B. H. CHASE and JAMES WALKER 3548

714. The Kinetics and Mechanisms of Nucleophilic Displacements in Allylic Systems. Part IV. The Reaction of 1 : 1-Dimethylallyl Chloride with the Thiophenoxide Ion.
By P. B. D. DE LA MARE and C. A. VERNON 3555

715. Addition of Free Radicals to Unsaturated Systems. Part IV. The Direction of Radical Addition to Hexafluoropropene.
By R. N. HASZELDINE 3559

716. Addition of Free Radicals to Unsaturated Systems. Part V. The Direction of Addition to 1 : 1-Difluoroprop-1-ene, 3 : 3 : 3-Trifluoro-2-trifluoromethylprop-1-ene, and 3-Chloro-3 : 3-difluoro-2-trifluoromethylprop-1-ene.
By R. N. HASZELDINE 3565

717. Trans-esterification as a Means of Halide Esterification under Neutral Conditions.
By W. M. CORBETT and J. KENNER 3572

719. The Oxidation of Carboxylic Acids containing a Tertiary Carbon Atom. Part II.
By J. KENYON and M. C. R. SYMONS 3580

720. Carcinogenic Nitrogen Compounds. Part XV. New Polysubstituted Angular Benzacridines and Benzophenarsazines.
By NG. PH. BUU-HOÏ, R. ROYER, M. HUBERT-HABART, and P. MABILLE . . 3584

721. Studies of *Aspergillus niger*. Part II. Transglycosidation by *Aspergillus niger*.
By S. A. BARKER and T. R. CARRINGTON 3588

722. Heterocyclic Imines and Amines. Part II. Derivatives of *iso*Indoline and *iso*Indolenine.
By P. F. CLARK, J. A. ELVIDGE, and R. P. LINSTEAD 3593

723. Furanochromones derived from Quinol.
By G. R. RAMAGE and C. V. STEAD. 3602

724. Perfluoroalkyl Grignard and Grignard-type Reagents. Part III. Heptafluoro-*n*-propylzinc iodide.
By R. N. HASZELDINE and E. G. WALASCHEWSKI 3607

725. Properties of Periodate-oxidised Polysaccharides. Part I. The Preparation of Polymeric Substances containing Nitrogen from Oxidised Starches.
By VINCENT C. BARRY and P. W. D. MITCHELL 3610

PAGE

726. The Isomerism of the Oximes. Part XLIV. Alkylcinnamaldoximes, Aroylaldoximes, and the Action of Potassium Cyanide and Sodium Sulphite on Aldoximes and their *O*-Methyl Ethers.
By M. Benger and O. L. Brady 3612

728. Alkyl–Oxygen Fission in Carboxylic Esters. Part XII. 1-*o*-Methoxyphenylethyl and α-Naphthylphenylmethyl Compounds. The Relative Effects of the Introduction of *o*- and of *p*-Methoxyl Groups into Phenylmethyl Compounds.
By R. E. Dabby, A. G. Davies, J. Kenyon, and B. J. Lyons 3619

729. The Preparation of *o*-Aminophenyl Sulphates.
By E. Boyland, D. Manson, and Peter Sims 3623

730. A New Synthesis of 1 : 3-Diketones and the Preparation of 1-Keto-olefins by Means of Trifluoroacetic Anhydride as Condensing Agent.
By A. L. Henne and J. M. Tedder 3628

731. Properties of Periodate-oxidised Polysaccharides. Part II. The Structure of Some Nitrogen-containing Polymers.
By Vincent C. Barry and P. W. D. Mitchell 3631

732. The Preparation and Properties of Some Alkyl β-D-Glucopyranoside Tetranitrates.
By D. M. Shepherd 3635

733. Gladiolic Acid. Part III. The Structures of Nor*iso*gladiolic Acid, Dihydrogladiolic Acid, and Cyclopolic Acid.
By L. A. Duncanson, John Frederick Grove, and (Mrs.) J. Zealley . . 3637

734. Gladiolic Acid. Part IV. Synthesis of 5-Methoxy-6-methylphthalide.
By D. Gardner and John Frederick Grove 3646

735. Phthalaldehydes and Related Compounds. Part III. Synthesis of Deoxygladiolic Acid and Experiments relating to the Structure of Dihydrogladiolic Acid.
By J. J. Brown and G. T. Newbold 3648

736. Studies in the Pyrrocoline Series.
By E. D. Rossiter and J. E. Saxton 3654

737. Triterpene Resinols and Related Acids. Part XXVI. Oleana-9(11) : 13(18)-dienol and Oleana-9(11) : 18-dienol. The Conversion of β-Amyrin into Germanicol.
By J. M. Beaton, J. D. Johnson, L. C. McKean, and F. S. Spring . . . 3660

738. Triterpene Resinols and Related Acids. Part XXVII. The Non-saponifiable Fraction from *Strychnos nux-vomica* Seed Fat : The Structure of *cyclo*Artenol.
By H. R. Bentley, J. A. Henry, D. S. Irvine, and F. S. Spring . . . 3673

740. Steroids. Part VI. Partial Synthesis of 9 : 11-Dehydroprogesterone.
By A. Ruff, C. W. Shoppee, and (in part) G. H. R. Summers 3683

742. The Chemistry of Extractives from Hardwoods. Part XIII. Colourless Constituents of *Pterocarpus* Species.
By F. E. King, C. B. Cotterill, D. H. Godson, L. Jurd, and T. J. King . . 3693

743. The Mechanism of the Schmidt Reaction with *o*-Benzoylbenzoic Acid.
By C. L. Arcus and M. M. Coombs. 3698

744. Cinnolines. Part XXXII. Further Experiments on the Effects of Heterocyclic Nuclei as Substituents in the Widman–Stoermer Synthesis.
By A. J. Nunn and K. Schofield. 3700

Notes :

745. Cinnolines. Part XXXIII. Some 3-Aryl-4-hydroxycinnolines.
By D. W. Ockenden and K. Schofield 3706

746. A New Synthesis of Arsonic Acids. Part IV. Stilbene-3-arsonic Acid.
By Walter Freund and Alfred Komzak 3707

747. Studies with Phenylbutadiene. Part I. A New Synthesis of Naphthalene.
By S. A. Faseeh. 3708

749. The Synthesis of Monofluorocitric Acid.
By D. E. A. Rivett 3710

750. A Method of Iodination.
By K. T. Potts 3711

754. Preparation of 2 : 3-Dihydro-3-oxobenzo-1 : 4-thiazine Derivatives as Possible Anthelmintics. Part II.
By Alexander Mackie and A. Anthony Cutler 3716

755. Phenylthiohydantoins from Serine and Threonine.
By V. M. Ingram. 3717

756. Azulenes. Part I. A Synthesis of Azulene.
By Douglas Lloyd and Frederick Rowe 3718

PAGE

757. Constituents of the Higher Fungi. Part III. Agrocybin.
By E. R. H. JONES and J. D. BU'LOCK 3719

758. A Convenient Synthesis of Some 4-Substituted 5-Aminopyrimidines.
By PHYLLIS D. LANDAUER and H. N. RYDON 3721

759. Methanesulphonic Anhydride.
By L. N. OWEN and S. P. WHITELAW 3723

760. The Condensation of Glyoxal and *iso*Nicotinoylhydrazine (Isoniazid).
By VINCENT C. BARRY and P. W. D. MITCHELL 3723

761. Ring Fision of 2-Cyano-1 : 2 : 3 : 4-tetrahydro-2-methyl-1-oxonaphthalene.
By D. B. COWELL, W. H. LINNELL, and D. W. MATHIESON 3725

762. Transfer of Hydride Ion.
By G. BADDELEY and W. PICKLES. 3726

OBITUARY NOTICE :

EDWARD HOPE 3730

INDEX OF AUTHORS' NAMES.

ANDERSEN, F. A. See Callomon, H. J., 3709.
Arcus, C. L., and Coombs, M. M., 3698.
Augood, D. R., Cadogan, J. I. G., Hey, D. H., and Williams, G. H., 3412.
Baddeley, G., and Pickles, W., 3726.
Bak, B. See Callomon, H. J., 3709.
Barker, S. A., and Carrington, T. R., 3588.
Barry, V. C., and Mitchell, P. W. D., 3610, 3631, 3723.
Beaton, J. M. Johnston, J. D., McKean, L. C., and Spring, F. S., 3660.
Bell, C. F. See Irving, H., 3538.
Bell, J., Hill, T., Macdonald, K. A., Reed, R. I., and Macdonald, A., 3456.
Bell, J., Macdonald, K. A., and Reed, R. I., 3459.
Bell, R. P., and Pearson, R. G., 3443.
Benger, M., and Brady, O. L., 3612.
Bentley, H. R., Henry, J. A., Irvine, D. S., and Spring, F. S., 3673.
Boyland, E., Manson, D., and Sims, P., 3623.
Brady, O. L. See Benger, M., 3612.
Brown, D. A., and Hudson, R. F., 3352.
Brown, J. J., and Newbold, G. T., 3648.
Brown, L. O., and Soper, F. G., 3576.
Buckingham, A. D., and Le Fèvre, R. J. W., 3432.
Bu'Lock, J. D. See Jones, E. R. H., 3719.
Buu-Hoï, Ng. Ph., Royer, R., Hubert-Habart, M., and Mabille, P., 3584.
Cabell, M. J. See Irving, H., 3417.
Cadogan, J. I. G. See Augood, D. R., 3412.
Callomon, H. J., Thompson, H. W., Andersen, F. A., and Bak, B., 3709.
Campbell, N., and Woodham, A. A., 3429.
Carrington, T. R. See Barker, S. A., 3588.
Carruthers, W., 3486.
Cavell, E. A. S., and Chapman, N. B., 3392.
Chakravarti, D., Chakravarti, R. N., and Chakravarti, S. C., 3337.
Chakravarti, R. N. See Chakravarti, D., 3337.
Chakravarti, S. C. See Chakravarti, D., 3337.
Chapman, N. B. See Cavell, E. A. S., 3392.
Chase, B. H., and Walker, J., 3518, 3548.
Clark, P. F., Elvidge, J. A., and Linstead, R. P., 3593.
Coombs, M. M. See Arcus, C. L., 3698.
Corbett, W. M., and Kenner, J., 3572.
Cotterill, C. B. See King, F. E., 3693.
Cowell, D. B., Linnell, W. H., and Mathieson, D. W., 3725.
Crawford, M., and Shaw, J. A. M., 3435.
Cromartie, R. I. T., and Harley-Mason, J., 3525.
Crombie, L., Hancock, J. E. H., and Linstead, R. P., 3496.
Cutler, A. A. See Mackie, A., 3716.
Dabby, R. E., Davies, A. G., Kenyon, J., and Lyons, B. J., 3619.
Davies, A. G. See Dabby, R. E., 3619.
Davison, W. H. T., 3712.
de la Mare, P. B. D., and Vernon, C. A., 3555.
Duncanson, L. A., Grove, John Frederick, and Zealley, J., 3637.
Edwards, W. G. H., and Hodges, R., 3427.
El Khadem, H., 3452.
Elton, G. A. H., and Mitchell, J. W., 3690.
Elvidge, J. A. See Clark, P. F., 3593.
El Wakkad, S. E. S. and Emara S. H., 3504, 3508.
Emara, S. H. See El Wakkad, S. E. S. 3504, 3508.
Emerson, K. See Whipple, R. O., 3715.
Faseeh, S. A., 3708.
Ford, M. C., Hunt, L. J., and Waters, W. A., 3529.
Freund, W., and Komzak, A., 3707.
Gardner, D., and Grove, John Frederick, 3646.
Godson, D. H. See King, F. E., 3693.
Grove, John Frederick. See Duncanson, L. A., 3637, and Gardner, D., 3646.
Hancock, J. E. H., and Linstead, R. P., 3490.
Hancock, J. E. H. See also Crombie, L., 3496.
Harley-Mason, J. See Cromartie, R. I. T., 3525.
Haszeldine, R. N., 3371, 3559, 3565.
Haszeldine, R. N., and Walaschewski, E. G., 3607.
Henne, A. L., and Tedder, J. M., 3628.
Henry, J. A. See Bentley, H. R., 3673.
Hey, D. H. See Augood, D. R., 3412.
Hill, T. See Bell, J., 3456.
Hinshelwood, Sir C. See Newton, S. A., 3384, and Phillips, L. S., 3679.
Hodges, R. See Edwards, W. G. H., 3427.
Holstead, C., and Lamberton, A. H., 3349.
Holstead, C., Lamberton, A. H., and Wyatt, P. A. H., 3341.
Hope, A. J. N., and Mitchell, S., 3483.

Horn, D. H. S., and Hougen, F. W., **3533**.
Hougen, F. W. See Horn, D. H. S., **3533**.
Hubert-Habart, M. See Buu-Hoï, Ng. Ph., **3584**.
Hudson, R. F. See Brown, D. A., **3352**.
Hunt, L. J. See Ford, M. C., **3529**.
Ingram, V. M., **3717**.
Irvine, D. S. See Bentley, H. R., **3673**.
Irving, H., and Bell, C. F., **3538**.
Irving, H., Cabell, M. J., and Mellor, D. H., **3417**.
Irving, H., and Rossotti, H. S., **3397**.
Johnston, J. D. See Beaton, J. M., **3660**.
Jones, E. R. H., and Bu'Lock, J. D., **3719**.
Jurd, L. See King, F. E., **3693**.
Kenner, J. See Corbett, W. M., **3572**.
Kenyon, J., and Symons, M. C. R., **3580**.
Kenyon, J. See also Dabby, R. E., **3619**.
King, F. E., Cotterill, C. B., Godson, D. H., Jurd, L., and King, T. J., **3693**.
King, T. J. See King, F. E., **3693**.
Komzak, A. See Freund, W., **3707**.
Kurzer, F., **3360**.
Lamberton, A. H. See Holstead, C., **3341**, **3349**.
Landauer, P. D., and Rydon, H. N., **3721**.
Le Fèvre, R. J. W. See Buckingham, A. D., **3432**.
Linnell, W. H. See Cowell, D. B., **3725**.
Linstead, R. P. See Clark, P. F., **3593**, Crombie, L., **3496**, and Hancock, J. E. H., **3490**.
Lloyd, D., and Rowe, F., **3718**.
Lyons, B. J. See Dabby, R. E., **3619**.
Mabille, P. See Buu-Hoï, Ng. Ph., **3584**.
Macbeth, A. K., and Robertson, W. G. P., **3512**.
Macdonald, A. See Bell, J., **3456**.
Macdonald, K. A. See Bell, J., **3456**, **3459**.
McKean, L. C. See Beaton, J. M., **3660**.
Mackie, A., and Cutler, A. A., **3716**.
Malkin, T., and Poole, A. G., **3470**.
Mansberg, E., and Shaw, G., **3467**.
Manson, D. See Boyland, E., **3623**.
Mathieson, D. W. See Cowell, D. B., **3725**.
Mellor, D. H. See Irving, H., **3417**.
Mitchell, J. W. See Elton, G. A. H., **3690**
Mitchell, P. W. D. See Barry, V. C., **3610**, **3631**, **3723**.
Mitchell, S. See Hope, A. J. N., **3483**.
Moore, R. F., and Waters, W. A., **3405**.
Neill, K. G., **3454**.
Newbold, G. T. See Brown, J. J., **3648**.
Newton, S. A., Stubbs, F. J., and Hinshelwood, Sir C., **3384**.
Nunn, A. J., and Schofield, K., **3700**.
Ockenden, D. W., and Schofield, K., **3440**, **3706**.
Owen, L. N., and Whitelaw, S. P., **3723**.
Peacock, R. D., **3617**.
Pearson, R. G., See Bell, R. P., **3443**.
Phillips, L. S., and Hinshelwood, Sir C., **3679**.
Pickles, W. See Baddeley, G., **3726**.
Poole, A. G. See Malkin, T., **3470**.
Potts, K. T., **3711**.
Pugh, W., **3445**.
Ramage, G. R., and Stead, C. V., **3602**.
Reed, R. I. See Bell, J., **3456**, **3459**.
Rivett, D. E. A., **3710**.
Robertson, W. G. P. See Macbeth, A. K., **3512**.
Rossiter, E. D., and Saxton, J. E., **3654**.
Rossotti, H. S. See Irving, H., **3397**.
Rowe, F. See Lloyd, D., **3718**.
Royer, R. See Buu-Hoï, Ng. Ph., **3584**.
Ruff, A., Shoppee, C. W., and Summers, G. H. R., **3683**.
Rydon, H. N. See Landauer, P. D., **3721**.
Saxton, J. E. See Rossiter, E. D., **3654**.
Schofield, K. See Nunn, A. J., **3700**, and Ockenden, D. W., **3440**, **3706**.
Shaw, G., **3464**.
Shaw, G. See also Mansberg, E., **3467**.
Shaw, J. A. M. See Crawford, M., **3435**.
Sharpe, A. G., **3713**.
Shepherd, D. M., **3635**.
Shoppee, C. W. See Ruff, A., **3683**.
Sims, P. See Boyland, E., **3623**.
Skinner, H. A., and Tees, T. F. S., **3378**.
Soper, F. G. See Brown, L. O., **3576**.
Spring, F. S. See Beaton, J. M., **3660**, and Bentley, H. R., **3673**.
Stead, C. V. See Ramage, G. R., **3602**.
Stubbs, F. J. See Newton, S. A., **3384**.
Summers, G. H. R. See Ruff, A., **3683**.
Sykes, W. O., **3543**.
Symons, M. C. R. See Kenyon, J., **3580**.
Tedder, J. M. See Henne, A. L., **3628**.
Tees, T. F. S. See Skinner, H. A., **3378**.
Thompson, H. W. See Callomon, H. J., **3709**.
Vernon, C. A. See de la Mare, P. B. D., **3555**.
Vincent, H. C. G., **3445**.
Walaschewski, E. G. See Haszeldine, R. N., **3607**.
Walker, J. See Chase, B. H., **3518**, **3548**.
Waters, W. A. See Ford, M. C., **3529**, and Moore, R. F., **3405**.
West, R. See Whipple, R. O., **3715**.
Whalley, W. B., **3366**, **3479**.
Whitelaw, S. P. See Owen, L. N., **3723**.
Whipple, R. O., West, R., and Emerson, K., **3715**.
Wilkins, C. J., **3409**.
Williams, G. H. See Augood, D. R., **3412**.
Woodham, A. A. See Campbell, N., **3429**.
Wyatt, P. A. H. See Holstead, C., **3341**.
Zealley, J. See Duncanson, L. A., **3637**.

NOTICES TO AUTHORS OF PAPERS

Sicentific communications for the *Journal* should be addressed to " The Honorary Secretaries, The Chemical Society, Burlington House, London, W.1." Papers to be read before a meeting of the Society are selected by the Honorary Secretaries.

A paper is not normally considered for publication in the *Journal* unless at least one of the authors is a Fellow of the Society, but in exceptional circumstances the Council is prepared to consider papers submitted by non-Fellows.

Communications that have appeared or have been accepted for publication with essentially the same scientific content in another Journal or freely available printed work shall not be published in the *Journal* of the Society unless this course is approved by the Council.

Papers are accepted by the Society on the understanding that the authors have obtained any necessary authority to publish.

The Society reserves the right to retain all papers sent to it, and authors are therefore advised to keep copies. When papers have been accepted for publication the authors are not at liberty, save by permission of the Council, to withdraw or delay them, or to publish them elsewhere until they have appeared in the *Journal* of the Society. Papers which are retained by the Council after being judged unsuitable for publication in the *Journal* are deposited in the Archives of the Society; this right is not usually exercised in regard to illustrations.

Authors are solely responsible for the factual accuracy of their papers. They are particularly requested to verify references.

Authors are requested to see that their papers conform, as nearly as possible, to the normal conventions of the *Journal*. It is essential that drawings and photographs be presented in the style required by the Society. Every paper must be prefaced by a short summary, but " Notes " do not require a summary. Authors should consult the brochure entitled " The Presentation of Papers for the Journal of the Chemical Society " for detailed instructions and advice on these and cognate matters; Fellows of the Society are entitled to one copy each, gratis, on application to the General Secretary, The Chemical Society, Burlington House, London, W.1; further copies may be obtained at the public price which is 1*s.* 6*d.* each, post free, or 12*s.* 6*d.* per 10 copies, post free.

Authors are expected to be familiar with the normal rules of nomenclature, but are invited to communicate with the Editor if in doubt or in special cases. Some of the principles followed are reviewed in " Modern Chemical Nomenclature," by Dr. Clarence Smith (*J.*, 1936, 1067) (6*d.* post free), and in the Editorial Reports on Nomenclature (*J.*, 1950, 3699; 1951, 3515; 1952, 5057) (1*s.* each post free). Much valuable discussion will be found in " British Chemical Nomenclature," by Dr. A. D. Mitchell [Edward Arnold and Co., 1948]. Authors should choose their symbols from the " Report by the Symbols Committee of the Royal Society representing the Royal Society, the Chemical Society, the Faraday Society, and the Physical Society, 1951 " (*J.*, 1951, 1677) [9*d.* per copy or 12*s.* per 25 copies (post free), obtainable from the General Secretary, The Chemical Society].

Authors will be expected to pay the cost of any considerable changes made by them in proof, apart from the correction of printers' errors.

Each author, or joint author, receives 10 preprints (without covers) free of charge. A quotation for extra preprints and an order form will be sent with the proofs. The order form (and any necessary remittance) must be returned with the proofs and the MS. to the Editor.

INFORMATION FOR CANDIDATES FOR FELLOWSHIP

The Chemical Society was founded in 1841 and received a Royal Charter in 1848.

The main function of the Society is to foster original research in chemistry and to facilitate the discussion and dissemination of new knowledge in all branches of the science.

Fellowship of the Society is open to men and women of all nationalities who are interested in chemistry and wish to keep in touch with its advances. Fellows are elected by the Council.

PRIVILEGES

Fellows paying the Annual Subscription of £4 10*s*. have the following privileges

To receive a selection of the publications of the Society to a value of £3 0*s*. without further payment.

To purchase additional publications at favourable prices.

To attend all meetings, discussions and lectures of the Society and to introduce two guests.

To consult and borrow books in the Library. Books may be borrowed by post.

To apply for grants from the Research Fund.

To submit papers for publication in the *Journal*.

Fellows under 27 years of age may pay £1 15*s*. per annum and receive :

The *Proceedings*, *Annual Reports on the Progress of Chemistry*, and *Quarterly Reviews* without further payment.

The right to purchase other publications at favourable prices.

All the other privileges of Fellowship.

LIBRARY

The extensive reference and lending library of the Chemical Society contains over 50,000 volumes dealing with every aspect of chemistry and with many branches of related sciences. The library is open on Monday to Friday from 10 a.m. to 9 p.m., and on Saturdays from 10 a.m. to 5 p.m.

Books available on loan may be sent by post to Fellows residing in Great Britain or Ireland.

MEETINGS

(*a*) *In London*.—Scientific Meetings of the Society are usually held on two Thursdays in each month from October to June at Burlington House, at which papers dealing with original work are read and discussed, organised discussions on subjects of current interest are arranged, and lectures by eminent British and foreign chemists are delivered.

(*b*) *Outside London*.—Scientific Meetings and lectures arranged by the Society's Local Representatives are also held outside London, and form an important part of the activities of the Society.

RESEARCH FUND

A Research Fund is available for the assistance of chemical research, and sums amounting annually to about £700 are granted for this purpose. Application for grants must be made on the appropriate form, which may be obtained from the General Secretary.

A brochure describing the activities of the Society and forms of application for Fellowship can be obtained from The General Secretary, The Chemical Society, Burlington House, Piccadilly, London, W.1.

670. *Alkaloids of* Glycosmis arborea. *Part I. Isolation of Arborine and Arborinine: The Structure of Arborine.*

By (Mrs.) D. Chakravarti, R. N. Chakravarti, and S. C. Chakravarti.

Arborine, $C_{16}H_{14}ON_2$, and arborinine, $C_{16}H_{15}O_4N$, have been isolated from the leaves of *Glycosmis arborea* in 0·5% and 0·12% yield respectively. The former is identified by degradation and synthesis as 2-benzyl-1-methylquinazol-4-one.

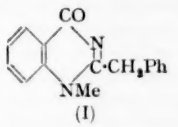
Mature leaves of *Glycosmis arborea* Correa are extensively used in the Ayurvedic system of medicine as, *e.g.*, a febrifuge and anthelmintic. From them arborine, $C_{16}H_{14}ON_2$ (m. p. 155—156°), and arborinine, $C_{16}H_{15}O_4N$ (m. p. 175—176°), were isolated in 0·5% and 0·07% yield, respectively, by R. N. Chakravarti and S. C. Chakravarti (*J. Inst. Chem., India*, 1952, **24**, 96); the yield of the latter has now been raised to 0·12%.

Chatterjee and Ghosh Majumdar (*Science and Culture*, 1952, **17**, 306) reported isolation of skimmianine (m. p. 175—176°) (yield, 0·03%) and an unidentified alkaloid (m. p. 225°) (yield, 0·003%) from leaves of a plant termed by them *G. pentaphylla*. Leaf fragments kindly supplied by them have been identified by us as *G. arborea* (Narayanswami, *Rec. Bot. Survey India*, 1941, **14**, No. 2; cf. Chakravarti and Chakravarti, *loc. cit.*), and 6 g. thereof yielded 20 mg. of arborine. This has been confirmed by Chatterjee and Ghosh Majumdar (*Science and Culture*, 1953, **18**, 505), who however used the name "glycosin" and ascribe to the alkaloid the erroneous formula $C_{15}H_{12}ON_2$.

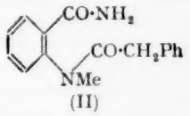
Arborine is optically inactive and contains one *N*-methyl but no methoxyl group. It is a weak monoacid tertiary base, yielding a picrate and a hydrochloride, the latter losing hydrochloric acid at 140° in a vacuum. When heated with selenium, arborine decomposes, without formation of hydrogen selenide, to yield a minute amount of an unidentified material. On distillation with soda-lime it yields ammonia, toluene, and methylaniline, indicating the presence of two benzene rings in the molecule.

Arborine is stable to water at 180° (10 hours) and to boiling concentrated hydrochloric acid (12 hours) and 50% sulphuric acid. In boiling 20% aqueous potassium hydroxide it affords 1 mol. each of *N*-methylanthranilic acid, phenylacetic acid, and ammonia, along with 0·05 mol. of a product, arboricine, $C_{16}H_{13}O_2N$. Use of aqueous barium hydroxide or alcoholic potassium hydroxide led to similar products, except that with shorter reaction times some of the *N*-methylanthranilic acid was recovered as its amide. Arborine thus contains the groupings (*o*-)NMe·C_6H_4·C$\leqslant$ and Ph·CH_2·C$\leqslant$.

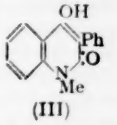
Hydrogenation converts arborine into a dihydro-derivative which has ill-defined basic character, separating unchanged on dilution of its solution in concentrated hydrochloric acid. Dihydroarborine is extremely stable to alkali but is hydrolysed by hot dilute hydrochloric acid, giving phenylacetaldehyde almost quantitatively, together with small amounts of *N*-methylanthranilic acid and the amide thereof. Arborine thus is 2-benzyl-1-methylquinazol-4-one (I), and dihydroarborine is the 2 : 3-dihydro-derivative thereof.



(I)



(II)



(III)

This identification was confirmed by synthesis. Phenylacetyl chloride and N^4-methylanthranilamide in cold pyridine gave the derivative (II), which when heated at 170—190° for ½ hour afforded arborine in almost quantitative yield.

The minor degradation product, arboricine, $C_{16}H_{13}O_2N$, was shown to be 1 : 2-dihydro-4-hydroxy-1-methyl-2-oxo-3-phenylquinoline (or its diketo-tautomer) by synthesis from ethyl phenylmalonate and *N*-methylaniline. Its formation from arborine probably occurs by way of (II) and the corresponding acid.

The alkaloid, arborinine, contains one methoxyl as well as one *N*-methyl group, and is optically inactive, but its structure is not further known.

Quinazolones are rare in Nature. Others isolated are evodiamine, rutaecarpine, and febrifugine (Koepfli, Mead, and Brockman, *J. Amer. Chem. Soc.*, 1949, **71**, 1048; Hutchings, Gordon, Ablondi, Wolf, and Willams, *J. Org. Chem.*, 1952, **17**, 19).

Experimental

Arborinine and Arborine.—Air-dried, powdered, mature leaves (1 kg.) of *Glycosmis arborea* (Chakravarti and Chakravarti, *loc. cit.*) were percolated with 90% alcohol. The residue obtained on evaporation of the solvent under reduced pressure was extracted with 2% hydrochloric acid (1 l.), and the acid extract (A) was washed with ether. The ethereal solution on evaporation gave yellow needles of almost pure arborinine. The pasty residue left after acid extraction was washed free from acid, treated with some alcohol, mixed with paper pulp, dried, and extracted (Soxhlet) first with light petroleum (b. p. 40—60°) for 8 hr. and then with ether for 16 hr. The petroleum extract on evaporation gave a dark viscous oil (32 g.), and the ethereal extract gave a dark sticky mass containing yellow needles. The ethereal extract was dissolved in hot concentrated hydrochloric acid (25 c.c.), allowed to cool, and filtered; this process was repeated until the acid filtrate was only light green. The residue, consisting of yellow needles with some adhering dark material, was washed with water, dried, and chromatographed in chloroform on aluminium oxide, with chloroform as the eluant. Evaporation of the chloroform gave a second crop of yellow needles of arborinine. The yields of the individual crops varied greatly but the total yield was usually about 0·12%. When purified by crystallisation from a large volume of absolute alcohol, it had m. p. 175—176° [Found : C, 67·3, 67·6; H, 5·2, 5·3; N, 5·1, 5·2; NMe, 10·2; OMe, 12·5%; *M* (Rast), 283. Calc. for $C_{16}H_{15}O_4N$: C, 67·4; H, 5·3; N, 4·9; 1NMe, 10·2; 1OMe, 10·9%; *M*, 285]. Arborinine gives a deep green colour with alcoholic ferric chloride; it readily dissolves in cold concentrated hydrochloric acid but immediately separates on dilution in small yellow needles which appear to be those of arborinine.

The acid extract (A) was treated as described previously (Chakravarti and Chakravarti, *loc. cit.*) for the isolation of arborine. Arborine (5 g.) obtained in this way was purified by repeated crystallisation from benzene containing a little absolute alcohol (charcoal). It crystallises in colourless rhombic plates with one molecule of benzene which it loses when kept. The solvent-free product melts at 155—156°. Arborine does not give any marked colour with aqueous or alcoholic ferric chloride, is a weak tertiary base, and does not react with nitrous acid. It has a slightly bitter taste and is highly soluble in alcohol [Found in material dried at 80° : C, 76·6, 76·7; H, 5·7, 5·8; N, 11·1, 11·2; NMe, 8·6; OMe, 0%; *M* (Rast), 276. Calc. for $C_{16}H_{14}ON_2$: C, 76·8; H, 5·6; N, 11·2; 1NMe, 11·6%; *M*, 250].

Arborine hydrochloride crystallises from water in colourless prisms, which melt partially at 106—108°, then resolidify, and remelt at 215° [Found : C, 58·9; H, 6·2; N, 9·5%; equiv. (titration with NaOH), 315·2. $C_{16}H_{14}ON_2,HCl,2H_2O$ requires C, 59·5; H, 5·9; N, 8·7%; equiv., 322·5]. As this salt is easily purified, the base can be conveniently purified through it.

Arborine picrate crystallises from alcohol in yellow needles, m. p. 172—173° (Found : C, 55·6; H, 3·6; N, 15·0. $C_{16}H_{14}ON_2,C_6H_3O_7N_3$ requires C, 55·1; H, 3·6; N, 14·6%).

Soda-lime Distillation of Arborine.—Benzene-free arborine (5·0 g.) and dry soda-lime (50 g.) were heated with a free flame in a distilling flask provided with a thermometer, the side arm being connected as for a distillation. The temperature was kept at about 100° for some time and then at 180—190°. The distillate, consisting of water and some oil and smelling strongly of ammonia, was shaken with ether. The ethereal solution was washed with water to remove ammonia, then extracted with 10% hydrochloric acid (acid extract B). The ethereal solution, after a final washing with water, was fractionated, giving a colourless liquid, b. p. 108—110° (0·4 g.), shown to be toluene by oxidation to benzoic acid with potassium permanganate.

The acid extract B was made alkaline with aqueous sodium hydroxide and the precipitated oil was taken up in ether, washed with water, and dried (Na_2SO_4). The oily liquid obtained on evaporation was distilled, giving a liquid, b. p. 190—191° (1·0 g.), identified as methylaniline by conversion into *N*-methylacetanilide.

Selenium Dehydrogenation of Arborine.—Arborine (1·0 g.) and selenium powder (3·0 g.) were heated gradually to 300° and then kept at 300—320° for 4 hr. No hydrogen selenide could be detected. A minute quantity of solid was deposited near the bottom of the condenser, and after resublimation and crystallisation from aqueous alcohol had m. p. 220—235°. The amount was insufficient for further work.

Hydrolysis of Arborine with Alkali.—Arborine (5·0 g.) was refluxed for 5 hr. with 10% alcoholic potassium hydroxide. The alcohol was then evaporated off with occasional addition of water to keep the volume constant. Much ammonia was evolved. On cooling, colourless needles of N^4-methylanthranilamide separated. These were collected (0·6 g.) (filtrate C); recrystallised from aqueous alcohol (charcoal), they had m. p. and mixed m. p. 160° (Found: C, 64·4; H, 6·7; N, 18·4; NMe, 16·5. Calc. for $C_8H_{10}ON_2$: C, 64·0; H, 6·7; N, 18·6; 1NMe, 19·3%). They gave a nitroso-compound with nitrous acid and lost ammonia when heated in concentrated aqueous sodium hydroxide.

The aqueous solution (C) was extracted three times with ether, and the aqueous solution (D) was kept for further treatment. The ethereal solution was extracted with 5% hydrochloric acid (15 c.c.) and then washed with a little water. On evaporation, a minute quantity of a neutral solid was obtained having a fragrant smell, but this was not identified. The acid extract, when made alkaline with sodium hydroxide solution and extracted with ether, gave N^4-methylanthranilamide (0·05 g.).

The aqueous solution (D) was strongly acidified with concentrated hydrochloric acid. Arboricine, which was precipitated, was collected (0·2 g.) (filtrate E) and crystallised from aqueous alcohol (charcoal) in colourless needles, m. p. 221—222° [Found: C, 76·4; H, 5·2; N, 5·5; NMe, 9·5%; *M* (Rast), 257. Calc. for $C_{16}H_{13}O_2N$: C, 76·5; H, 5·2; N, 5·6; NMe, 11·5%; *M*, 251]. It does not evolve carbon dioxide from sodium hydrogen carbonate solution but dissolves in sodium hydroxide solution. It dissolves in hot concentrated hydrochloric acid from which it crystallises unchanged on cooling.

The aqueous filtrate (E) was nearly neutralised (litmus) with sodium hydroxide solution. A colourless precipitate was collected (0·5 g.) (filtrate F), and recrystallised from aqueous alcohol (charcoal), colourless needles being obtained, m. p. 179—180°, showing a blue fluorescence in ethereal, alcoholic, or aqueous solution. The fluorescence of the aqueous solution becomes deeper on addition of alkali and is discharged by acid. This product was amphoteric and was identified as *N*-methylanthranilic acid (mixed m. p.) (Found: C, 63·4; H, 5·8; N, 9·2; NMe, 14·1. Calc. for $C_8H_9O_2N$: C, 63·5; H, 5·9; N, 9·2; NMe, 19·2%).

The aqueous filtrate (F) was repeatedly extracted with ether. The semi-solid residue obtained on evaporation was dissolved in a minimum of hot 2% hydrochloric acid, filtered, and then cooled in ice. Phenylacetic acid which separated was collected (0·5 g.), and from the filtrate a further crop of *N*-methylanthranilic acid (0·06 g.) was obtained after neutralisation followed by extraction with ether. The phenylacetic acid was purified by several crystallisations from water (charcoal), and had m. p. and mixed m. p. 76° (Found: C, 70·5; H, 6·0. Calc. for $C_8H_8O_2$: C, 70·6; H, 5·9%).

In one experiment, hydrolysis of benzene-free arborine (1·0 g.) was carried out with hot 20% aqueous potassium hydroxide solution (25 c.c.) for about 4 hr. and the ammonia evolved was determined after absorption in standard acid (Found: NH_3, 6·9. Calc. for $C_{16}H_{14}ON_2$: $1NH_3$, 7·0%). From the alkaline solution approx. one molecular proportion each of *N*-methylanthranilic acid and phenylacetic acid along with a small quantity (0·05 g.) of arboricine were isolated.

Hydrolysis of arborine with hot saturated aqueous barium hydroxide gave smoothly *N*-methylanthranilic acid, N^4-methylanthranilamide, phenylacetic acid, and arboricine.

Dihydroarborine.—Purified benzene-free arborine (1·131 g.) was shaken in absolute alcohol (25 c.c.) with Adams catalyst (0·1 g.) under hydrogen [absorption, complete in 2·5 hr.: 104 c.c. (N.T.P.); one double bond requires 102 c.c.]. Crystals separated as soon as the hydrogen atmosphere above the solution was replaced by air. These were again brought into solution by the addition of sufficient amount of chloroform and heating. The mixture was then filtered and the filtrate was heated on the water-bath to remove most of the chloroform. On cooling, *dihydroarborine* separated in colourless plates, m. p. 199—200° (1·012 g.), and was purified by recrystallisation chloroform–alcohol [Found: C, 75·8; H, 6·1; N, 11·3%; *M* (Rast), 246. $C_{16}H_{16}ON_2$ requires C, 76·2; H, 6·3; N, 11·1%; *M*, 252]. It is insoluble in water and alcohol, slightly soluble in ether, and somewhat more soluble in chloroform and glacial acetic acid. It is insoluble in aqueous alkalis and in dilute acids, but dissolves in concentrated hydrochloric acid with the formation of a pale yellow solution from which it separates unchanged on dilution. In chloroform or ether it shows a violet fluorescence.

Dihydroarborine was also prepared by heating a solution of arborine in 10% hydrochloric acid at 45—50° for 24 hr. in presence of granulated zinc. A white precipitate which separated was extracted with chloroform. Evaporation to a small bulk and dilution with absolute alcohol gave a very small yield of dihydroarborine.

Hydrolysis of Dihydroarborine.—Dihydroarborine (0·5 g.) gave a pale yellow solution in concentrated hydrochloric acid (10 c.c.). This was diluted with water (20 c.c.) and distilled on a sand-bath, the volume being kept constant by addition of water. An oil with a fragrant smell (phenylacetaldehyde) collected in the distillate. Heating was stopped when the distillate was free from suspended oil. The distillate was extracted with ether, the extract washed with water, dried (Na_2SO_4), and the solvent evaporated, giving a fragrant light yellow oil. The yield of this appeared to depend on the heating and rate of distillation, but was sometimes almost quantitative. The oil readily gave phenylacetaldehyde semicarbazone, prisms (from dilute alcohol), m. p. 155—156°, and the 2 : 4-dinitrophenylhydrazone, m. p. 121°, identified by mixed m. p.s with authentic specimens.

The aqueous solution remaining in the distilling flask was filtered, extracted with ether (only a trace of gum removed), made alkaline with sodium hydroxide, and again extracted thoroughly with ether (aqueous solution G). On evaporation of the ether N^4-methylanthranilamide (40 mg.), m. p. and mixed m. p. 160° (from benzene or alcohol), were obtained.

The aqueous solution (G) was made just acid to Congo-red with hydrochloric acid and repeatedly extracted with ether, and the extract was washed with water and evaporated, yielding N^4-methylanthranilic acid, m. p. and mixed m. p. 179—180° (from aqueous alcohol) (50 mg.).

N^4-*Methyl*-N^4-*phenylacetylanthranilamide* (II).—*N*-Methylanthranilamide (1·0 g.) in anhydrous pyridine (10 c.c.) was treated at 0° with phenylacetyl chloride (2·0 g.) with shaking and kept overnight at room temperature. The product was treated with ice and set aside for about an hour, then acidified to Congo-red with concentrated hydrochloric acid to keep unchanged *N*-methylanthranilamide in solution. A gum which separated was extracted with chloroform, and the extract was washed successively with 5% hydrochloric acid, saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated. The crystalline residue was recrystallised from benzene, giving N^4-*methyl*-N^4-*phenylacetylanthranilamide* (II) as prisms, m. p. 159—160° (0·9 g.) (Found : C, 72·0; H, 6·0; N, 10·8. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0; N, 10·4%).

2-*Benzyl*-1-*methylquinazol*-4-*one* (I).—N^4-Methyl-N^4-phenylacetylanthranilamide (0·25 g.) was heated from 170° to 190° during 20 min. and then kept at 190° for about 10 min. Cyclisation took place with vigorous frothing. The product was dissolved in the minimum of hot absolute alcohol and the solution then diluted with benzene. Some of the benzene was allowed to evaporate, most of the alcohol being thus removed. On cooling, 2-*benzyl*-1-*methylquinazol*-4-*one* separated as colourless rhombic plates, m. p. 155—156° (0·2 g.). The crystals contain one molecule of benzene of crystallisation which they lose gradually. The solvent-free product appears to be amorphous (Found, in material dried at 80° : C, 76·7; H, 5·8; N, 11·3. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%).

A mixture of this and arborine in equal proportions melted sharply at 155—156°.

1 : 2-*Dihydro*-4-*hydroxy*-1-*methyl*-2-*oxo*-3-*phenylquinoline.*—Ethyl phenylmalonate (10 g.) and methylaniline (4 g.) were heated at 200—220° for 1½ hr. On cooling, crystals separated. Crystallised from aqueous alcohol these gave the *quinoline* derivative (III) as needles (1·5 g.), m. p. 222°, not depressed on admixture with arboricine (Found : C, 76·5; H, 5·3; N, 5·4. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%).

BETHUNE COLLEGE, CALCUTTA.
SCHOOL OF TROPICAL MEDICINE, CALCUTTA.

[*Received, partly, March* 23*rd*, 1953, *and, partly, April* 30*th*, 1953.]

671. *Nitramines and Nitramides. Part V.* Nitrations of Urethane, N-Methylurethane, Urea, and Hexahydro-1 : 3-dinitro-1 : 3 : 5-triazine in Sulphuric Acid.*

By C. Holstead, Alex. H. Lamberton, and (in part) P. A. H. Wyatt.

The nitrations of urethane, *N*-methylurethane, urea, and hexahydro-1 : 3-dinitro-1 : 3 : 5-triazine are reversible in sulphuric acid–water media; the position of equilibrium depends on the concentration of the acid. For urea and the hexahydrotriazine, as for guanidine (Simkins and Williams, *J.*, 1952, 3086), nitration reaches its maximum in 88% w/w sulphuric acid. The urethanes, however, show an increasing degree of nitration, though the equilibrium is established more slowly, as the acid concentration is decreased (88 ⟶ 75%, w/w). This difference (as between urea and urethane) may be due to differing degrees of salt formation, but neither cryoscopic measurements nor ultra-violet spectra provide proof.

In Part III (*J.*, 1952, 1886) we gave the qualitative results of the treatment of a wide variety of *N*-nitro-compounds with sulphuric acid. By arrangement with Professor Gwyn Williams, of whose work we learnt during the earlier research, we examined quantitatively a number of nitrations, but left the detailed investigation of the nitration of guanidine in sulphuric acid (Part I, Simkins and Williams, *J.*, 1952, 3086) to his laboratory.

In general, we added the *N*-nitro-compound to sulphuric acid–water mixtures of known composition, and determined, by the method of Simkins and Williams (*loc. cit.*), the nitric acid liberated. In some cases, to prove reversibility, we employed equimolar quantities of the amide and nitric acid, or a salt [*e.g.*, urea nitrate or hexahydro-1 : 3-dinitro-1 : 3 : 5-triazine nitrate (" P.C.X.") (I)] as initial materials. Minor modifications in technique are detailed in the Experimental section.

After dissolution of nitrourethane (0·2M) in a sulphuric acid–water mixture (75·4% H_2SO_4, w/w), the free nitric acid in the system rose, in about 5 hours at 25°, to 39% of the total potentially available. When equimolar quantities (0·2M) of urethane and nitric acid were used initially, the free nitric acid fell, in the same time, to 37% of its initial value. The equilibrium values are not precisely identical, since the nitric acid was added as concentrated (70% w/w) acid: the water thus introduced changed the initial solvent to 74·6% w/w sulphuric acid. In more concentrated acid equilibrium was established more rapidly. In 79·9% w/w sulphuric acid equilibration was complete in 40 minutes, whilst in 91·5% w/w sulphuric acid it was attained before the first observation was made (14 minutes after mixing).

In concentrated sulphuric acid the nitric acid content of the equilibrium mixtures fell slowly; this appears to be due to the irreversible decomposition of the *N*-nitro-compound to yield nitrous oxide. The reaction is distinct from, but concurrent with, the nitration–denitration equilibrium, and is under investigation. To allow for the loss of nitric acid occasioned indirectly by the irreversible decomposition of the *N*-nitro-compound, the experimental curves were extrapolated back to the time origin, and the figures thus obtained taken to indicate the true equilibrium proportion of free nitric acid in 0·2M-solutions at 25°. As nitric acid is stable, and the *N*-nitro-compound unstable, this is presumably an under-correction (*i.e.*, will not indicate sufficient nitric acid) whenever the *N*-nitro-compound was used as initial material; but, with three exceptions (indicated specifically in the Experimental section), we do not believe the error in the correction to be significant.

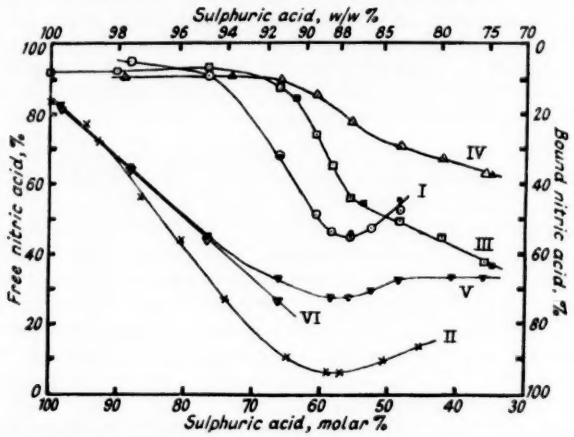
The Figure shows how the equilibrium proportions of nitric acid (evaluated, as indicated above, by extrapolation to zero time) varied with changes in the sulphuric acid–water solvent. It will be seen that urea (curve I), like guanidine (curve II, plotted from the results of Simkins and Williams, *loc. cit.*), showed a maximum degree of nitration in the optimum solvent (88% w/w sulphuric acid) for aromatic nitration, though the yield from

* Part IV, *J.*, 1953, 1998.

urea was far less favourable. The urethanes behaved differently. Here (curves III and IV), though the 88—85% w/w sulphuric acid region clearly marked a transition point in the curves, the proportion nitrated at equilibrium continued to increase in more dilute acid.

The qualitative difference between urea (or guanidine) and the urethanes may be due to differences in the nitration processes involved, or to differences in basic strength which might affect the nitration equilibrium. We do not favour the first of these hypotheses, though solely on the evidence (see Part VI) that in a less acidic solvent, *viz.*, acetic anhydride, urethane and urea are nitrated at similar speeds.

Equilibrium proportions of nitric acid at 25°.



I.	Nitrourea, 0·2M	○
	Urea nitrate, 0·2M	●
II.	Nitroguanidine, 0·2M	×
III.	Nitrourethane, 0·2M	⊡
	Urethane and nitric acid, each 0·2M	■
IV.	*N*-Methylnitrourethane, 0·2M	△
	N-Methylurethane and nitric acid, each 0·2M	▲
V.	Hexahydro-1 : 3-dinitro-1 : 3 : 5-triazine nitrate ("P.C.X."), 0·2/3M	▼
VI.	Cyclonite, 0·2/3M	▽

The second hypothesis can be discussed in terms of the following equilibria which may be involved :

$$\underset{(A)}{>\overset{+}{N}H_2} \underset{+H^+}{\rightleftharpoons} \underset{(B)}{>NH} \overset{+NO_2^+}{\rightleftharpoons} \underset{(C)}{>\overset{+}{N}H{\cdot}NO_2} \underset{+H^+}{\rightleftharpoons} \underset{(D)}{>N{\cdot}NO_2}$$

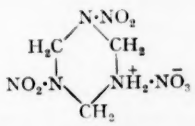
It has been shown by Wright (*Canad. J. Res.*, **1948**, **26**, 104, 114) that *N*-nitration is dependent on the basic strength of amines, and it appears that the corresponding ammonium salts cannot, as such, be nitrated. It seems, however, that guanidine is nitrated as the guanidinium ion; the positive charge shared between three nitrogen atoms is presumably less discouraging to nitration than the localised charge in salts of simple amines. Charge distribution may also permit the direct nitration of salts of urea. But salts of urethane, like those of simple amines, might well be resistant to nitration; and it was thought that if allowance were made for the urethane removed from the nitration equilibrium by salt formation, then the resultant curve might resemble those obtained from guanidine and from urea.

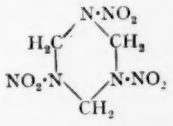
Cryoscopic measurements have therefore been made in sulphuric acid, and in sulphuric acid monohydrate. Urea and urethane gave identical depressions, within the limits of experimental error, in both solvents. In sulphuric acid (100% w/w) both were monoprotonated. In sulphuric acid monohydrate, a less suitable solvent, the indications were

less precise; but the identity of their behaviour and the known basic strength of urea suggested that here, too, salt formation from urethane was essentially complete. Ultraviolet absorption spectra have also been examined but were not diagnostic; there was no significant absorption either in aqueous or in sulphuric acid solutions.

The evidence, therefore, does not support the second hypothesis. Unfortunately, the converse is not true: consideration of the equilibria involved shows that the cryoscopic measurements do not afford positive disproof. If suitable (and by no means improbable) values are postulated for the ratios B/A and $B/(C + D)$, then changes in the B/A ratio corresponding to small alterations in the percentage of ionisation of the base (as from, say, 99 to 98%) would greatly decrease the value of the ratio free nitric acid/bound nitric acid $[(A + B)/(C + D)]$. Such small alterations could not be detected cryoscopically.

We consider that further discussion is not yet warranted, particularly since (1) differences in the (unknown) basic strengths of nitrourethane and nitrourea (≡ differences in the ratio C/D) might be significant, and (2) we cannot exclude the possibility that a salt of urethane can be nitrated directly—*i.e.*, without passing through the base. Wright's work (*loc. cit.*) in acetic anhydride–acetic acid is rather far removed from the conditions we have employed; and it is to be noted that, even in 100% sulphuric acid, about 1/10th of the nitric acid potentially available from nitrourethane remains bound. We simply record, as evidence in favour of the second hypothesis (p. 3342), that urethane and *N*-methylurethane have been found, in water at least, to be much weaker bases than urea. This is at least consonant with our suggestion that, whilst urea is monoprotonated in 75—88% w/w sulphuric acid, the urethanes exist to a small, but varying, extent as free bases; and that the qualitative difference between curves I and II and curves III and IV is due to the less complete ionisation of the urethanes in more dilute (90 ⟶ 75% w/w) sulphuric acid.

(I) 

 (II)

When " P.C.X." (I) was dissolved in sulphuric acid of less than 80% w/w concentration, the nitric acid liberated corresponded simply to the nitrate content of the salt. In more concentrated (90—100%, w/w) sulphuric acid, nitric acid derived from the nitramino-groups was also liberated; if 3 molecular proportions of nitric acid are taken to be the potential (100%) yield, then as much as 82% of the total was liberated by 99·7% w/w sulphuric acid. Cyclonite (II) behaved similarly in concentrated (93—100% w/w) acid.

These results are presented graphically in the figure. The dip in the " P.C.X." curve around 88% w/w sulphuric acid is of particular interest. Here the free nitric acid found was less than that introduced, as nitrate, in the " P.C.X." It follows that in this region " P.C.X." must be partly converted into cyclonite: (I) and (II) are presumably in equilibrium. We have been able, using more concentrated solutions, to prepare cyclonite by the action of 88% w/w sulphuric acid upon " P.C.X."

Solutions of cyclonite, and of " P.C.X.," in sulphuric acid were not stable. Irreversible decomposition of the nitramino-groups occurs and, by equilibration, nitric acid is removed from the system. This explains why, apart from Part III of this series (*loc. cit.*), nitrous oxide, but not nitric acid, has been recognised as a product of the action of sulphuric acid upon cyclonite. Even in comparatively dilute (60% w/w) sulphuric acid, " P.C.X." was not indefinitely stable. After an induction period of *ca.* 10 hr. at 25°, a 0·067M-solution decomposed suddenly, and the nitric acid content fell, within an hour, from 0·065 to 0·005M. Irreversible decomposition is probably responsible also for the slight apparent difference between " P.C.X." and cyclonite in concentrated acid. Cyclonite, unlike " P.C.X.," dissolves slowly: the initial measurements could not be made so soon and the correction (see p. 3341) to zero time must be less reliable. In 91·5% w/w acid, 40 minutes elapsed before dissolution was complete and, though we report the value obtained, we regard it as only approximate.

Experimental

Materials.—The *N*-nitro-compounds were prepared by standard methods, or were given to us; for references and acknowledgments see Part III (*J.*, 1952, 1894).

Preparation of Hexahydro-1 : 3-dinitro-1 : 3 : 5-triazine Nitrate ("*P.C.X.*") (Hirst, Bevan, Carruthers, Dunning, Foss, Jones, and Sullivan, personal communication, 1943).—Freshly purified nitric acid (free from nitrous acid, 160 ml. of 98%) was placed in a 500-ml. bolt-head flask fitted with a mechanical stirrer, and cooled to −10° with acetone–carbon dioxide. Water (13·4 ml.) was added dropwise (temp. <0°), and the diluted (*ca.* 93%) acid then cooled to −40°. Hexamine dinitrate (20 g.) was added in 1 min. at −40°, and nitrolysis allowed to proceed for 10 min., in all, at −40°. Water (340 ml.) was then added streamwise in 7 min. with maintenance of the temperature at < −10°. The suspension in diluted acid was allowed to age, without cooling, for 5 min., and the prisms of *hexahydro-1 : 3-dinitro-1 : 3 : 5-triazine nitrate* (9 g.; m. p. 99°, decomp.) were collected on sintered glass, and washed with cold 50% nitric acid (twice), cold alcohol (twice), and ether (thrice) [Found (Hirst *et al.*): C, 15·1; H, 3·5; N, 34·6. $C_3H_7O_4N_5,HNO_3$ requires C, 15·0; H, 3·3; N, 35·0%]. Potentially available methylenedinitramine has been determined (*J.*, 1946, 1656), and the purity of the present sample was checked by the determination (with $FeSO_4$–HCl) of NO_3^- liberated in water or in aqueous sodium hydroxide (Found: NO_3^-, 25·6, 25·8. Calc.: NO_3^-, 25·8%).

Preparation of Solutions in Sulphuric Acid–Water Media, and Analysis.—The solutions were made and analysed by Simkins and Williams's method (*J.*, 1952, 3086). In this analysis nitrate is reduced to nitric oxide, in the absence of air, by boiling with an excess of standard ferrous sulphate in hydrochloric acid with ammonium molybdate as catalyst; the reaction is completed by expelling nitric oxide, and the residual ferrous salt titrated with potassium dichromate. When nitric acid and the amide (*e.g.*, urethane) were used as initial materials, the former was first added, as pure concentrated (70%) nitric acid, to sulphuric acid of known strength, and allowance was made for the water thus introduced. With the exception of cyclonite, all the compounds dissolved rapidly (<1 min.) in the solvents employed on being shaken by hand at room temperature; and the resultant solutions were brought to 25° within 5 min. of the start of the experiment.

Nitrourethane, *N*-methylnitrourethane, and nitrourea were destroyed (as was nitroguanidine in the paper cited) by boiling aqueous sodium hydroxide. If not so destroyed they affected the analysis, giving spurious indications of, respectively, 2, 17, and 2% of nitric acid. Cyclonite did not affect the analysis, but gave spurious indications of nitric acid after treatment with aqueous sodium hydroxide. "P.C.X." gave one molecular proportion of nitric acid with, or without, such treatment. Refluxing with aqueous sodium hydroxide was, therefore, not employed in the investigation of cyclonite or "P.C.X."

We employed the electrometric "dead stop" end-point in the titration of excess of ferrous sulphate with potassium dichromate, but have used Foulk and Bawden's simple circuit (*J. Amer. Chem. Soc.*, 1926, **48**, 2045), in conjunction with a Cambridge spot galvanometer (sensitivity 170 mm./μA): the end-point could be determined to ±0·01 ml. Our blank correction for the loss of ferrous ion was greater than that reported by Simkins and Williams, but was consistent at 0·0043 ± 0·0002M-nitrate.

Analytical Results.—In the Tables which follow our results are reported to 0·0001M-nitrate (≡0·01 ml. titration), but individual values are not printed for experiments in which the nitric acid content remained essentially constant (±0·001M) throughout: we consider the errors in analysis to be in most cases <0·0005M. Times (*t*, in min.) were measured from the initial mixing. The equilibrium values were obtained, as already described (p. 3341) by extrapolation to zero time. No allowance has been made for the water taken up, or set free, in the process of equilibration. For example, in Expt. 10 (half-denitration) the equilibrium solution presumably consisted of urethane, nitrourethane, and nitric acid dissolved in sulphuric acid of 83·73% w/w (initial value, as reported, 83·64% w/w).

Preparation of Cyclonite from "P.C.X." and Sulphuric Acid.—"P.C.X." (0·5 g.) was added, in 2 min. at 25°, to sulphuric acid (5 ml.; 88·5%, w/w). After 15 min. at 25°, the solution was poured on ice (25 g.), and the cyclonite (0·11 g.; m. p. 203°, decomp., undepressed by mixture with authentic material) collected.

Comparative Basic Strength of Urea and Urethanes in Dilute Hydrochloric Acid.—Solutions (0·290M in sucrose; 0·504, 0·495, and 0·491M in hydrochloric acid and in, respectively, urea, urethane, and *N*-methylurethane) were kept at 25°. The rate of inversion was determined by polarimetry, and compared with that given by hydrochloric acid alone. In detail we followed

TABLE 1. *Molarity of free* HNO_3 *obtained from nitrourethane* (0·2M) *in sulphuric acid–water mixtures at* 25° ± 0·2°.

Expt. 1. H_2SO_4, 100·0% w/w. Equil. val.: $[HNO_3]$ 0·183 (*t* 15 to 90).

Expts. 2, 3. H_2SO_4, 97·58% w/w. Equil. val.: $[HNO_3]$ 0·185 (*t* 15 to 88).

Expt. 4. H_2SO_4, 94·70% w/w. Equil. val.: $[HNO_3]$ 0·187 (*t* 15 to 88).

Expts. 5, 6.* H_2SO_4, 91·46% w/w. Equil. val.: $[HNO_3]$ 0·175.

t	14 *	20	25 *	33 *	34	43	45 *
$[HNO_3]$	0·1740	0·1736	0·1735	0·1729	0·1734	0·1728	0·1717
t	55 *	57	63	64 *	75 *	80	94
$[HNO_3]$	0·1719	0·1725	0·1716	0·1708	0·1699	0·1712	0·1699

Expt. 7. H_2SO_4, 89·47% w/w. Equil. val.; $[HNO_3]$ 0·148.

t	17	27	37	46	56	66
$[HNO_3]$	0·1460	0·1457	0·1449	0·1436	0·1438	0·1420

Expt. 8. H_2SO_4, 88·46% w/w. Equil. val.: $[HNO_3]$ 0·130.

t	19	28	40	50	61	70
$[HNO_3]$	0·1288	0·1284	0·1265	0·1266	0·1259	0·1251

Expt. 9. H_2SO_4, 87·26% w/w. Equil. val.: $[HNO_3]$ 0·112.

t	19	32	45	57	72	83	97
$[HNO_3]$	0·1116	0·1117	0·1117	0·1104	0·1101	0·1091	0·1074

Expt. 10. H_2SO_4, 83·64% w/w. Equil. val.: $[HNO_3]$ 0·099 (*t* 17 to 71).

Expt. 11. H_2SO_4, 79·88% w/w. Equil. val.: $[HNO_3]$ 0·089.

t	16	26	36	47	56	67	76	86
$[HNO_3]$	0·0784	0·0864	0·0884	0·0880	0·0876	0·0874	0·0872	0·0869

Expts. 12, 13.* H_2SO_4, 75·38% w/w. Equil. val.: $[HNO_3]$ 0·075.

t	13	28	37	50	60	72	82	90
$[HNO_3]$	0·0096	0·0209	0·0281	0·0366	0·0423	0·0479	0·0522	0·0552
t	112 *	133 *	159 *	192 *	221 *	277 *	401 *	
$[HNO_3]$	0·0619	0·0661	0·0695	0·0724	0·0738	0·0747	0·0747	

* In this and similar Tables, asterisks relate values of *t* to experiment numbers similarly marked.

TABLE 2. *Molarity of free* HNO_3 *obtained from urethane* (0·2M) *and* HNO_3 (0·2M) *in sulphuric acid–water mixtures at* 25° ± 0·2°.

Expt. 14. H_2SO_4, 90·55% w/w. Equil. val.: $[HNO_3]$ 0·169.

t	14	24	34	46	59	74	88
$[HNO_3]$	0·1681	0·1680	0·1671	0·1667	0·1658	0·1644	0·1644

Expt. 15. H_2SO_4, 86·40% w/w. Equil. val.: $[HNO_3]$ 0·109 (*t* 15 to 75).

Expt. 16. H_2SO_4, 74·57% w/w. Equil. val.: $[HNO_3]$ 0·073.

t	35	73	100	134	165	203	279	330
$[HNO_3]$	0·1289	0·1015	0·0909	0·0833	0·0793	0·0766	0·0751	0·0737
t	378	443	494					
$[HNO_3]$	0·0736	0·0730	0·0730					

TABLE 3. *Molarity of free* HNO_3 *obtained from* N*-methylnitrourethane* (0·2M) *in sulphuric acid–water mixtures at* 25° ± 0·2°.

Expt. 17. H_2SO_4, 97·58% w/w. Equil. val.: $[HNO_3]$ 0·181 (*t* 13 to 83).

Expt. 18. H_2SO_4, 94·70% w/w. Equil. val.: $[HNO_3]$ 0·181 (*t* 12 to 80).

Expt. 19. H_2SO_4, 91·46% w/w. Equil. val.: $[HNO_3]$ 0·179.

.....	14	25	38	51	66	85
$[HNO_3]$	0·1782	0·1768	0·1776	0·1769	0·1768	0·1758

Expt. 20. H_2SO_4, 89·47% w/w. Equil. val.: $[HNO_3]$ 0·171.

t	13	24	36	49	62	80
$[HNO_3]$	0·1702	0·1692	0·1684	0·1675	0·1669	0·1656

Expt. 21. H_2SO_4, 87·26% w/w. Equil. val.: $[HNO_3]$ 0·156.

t	13	25	36	48	60	75	90
$[HNO_3]$	0·1556	0·1547	0·1543	0·1547	0·1536	0·1530	0·1500

TABLE 3.—*Continued.*

Expt. 22. H_2SO_4, 83·64% w/w. Equil. val.: $[HNO_3]$ 0·142 (*t* 12 to 80).

Expt. 23. H_2SO_4, 79·88% w/w. Equil. val.: $[HNO_3]$ 0·135 (*t* 11 to 72).

Expt. 24. H_2SO_4, 75·38% w/w. Equil. val.: $[HNO_3]$ 0·126.

t	13	26	46	66	97	126
$[HNO_3]$	0·1182	0·1255	0·1256	0·1254	0·1253	0·1252

TABLE 4. *Molarity of free* HNO_3 *obtained from* N-*methylurethane* (0·2M) *and* HNO_3 (0·2M) *in sulphuric acid–water mixtures at* 25° ± 0·2°.

Expt. 25. H_2SO_4, 93·78% w/w. Equil. val.: $[HNO_3]$ 0·181 (*t* 12 to 75).

Expt. 26. H_2SO_4, 74·59% w/w. Equil. val.: $[HNO_3]$ 0·125.

t	11	23	35	51	65	85	116
$[HNO_3]$	0·1305	0·1251	0·1243	0·1237	0·1233	0·1223	0·1206

TABLE 5. *Molarity of free* HNO_3 *obtained from nitrourea* (0·2M) *in sulphuric acid–water mixtures at* 25° ± 0·2°.

Expt. 27. H_2SO_4, 97·58% w/w. Equil. val.: $[HNO_3]$ 0·190 (*t* 13 to 92).

Expt. 28. H_2SO_4, 94·70% w/w. Equil. val.: $[HNO_3]$ 0·182.

t	12	24	33	44	56	69	89
$[HNO_3]$	0·1808	0·1795	0·1776	0·1765	0·1761	0·1742	0·1712

Expt. 29. H_2SO_4, 91·46% w/w. Equil. val.: $[HNO_3]$ 0·136.

t	12	22	32	45	59	70
$[HNO_3]$	0·1334	0·1300	0·1269	0·1238	0·1206	0·1169

Expt. 30. H_2SO_4, 89·47% w/w. Equil. val.: $[HNO_3]$ 0·103.

t	13	28	38	48	57	75
$[HNO_3]$	0·0996	0·0956	0·0935	0·0908	0·0880	0·0835

Expt. 31. H_2SO_4, 88·46% w/w. Equil. val.: $[HNO_3]$ 0·093.

t	11	22	35	50	63	82
$[HNO_3]$	0·0905	0·0880	0·0858	0·0819	0·0796	0·0745

Expt. 32. H_2SO_4, 87·26% w/w. Equil. val.: $[HNO_3]$ 0·089.

t	12	21	35	48	60	73	90
$[HNO_3]$	0·0857	0·0849	0·0822	0·0801	0·0775	0·0745	0·0722

Expt. 33. H_2SO_4, 85·78% w/w. Equil. val.: $[HNO_3]$ 0·095.

t	11	22	34	45	57	75
$[HNO_3]$	0·0810	0·0905	0·0891	0·0869	0·0848	0·0811

Expt. 34. H_2SO_4, 83·64% w/w. Equil. val.: $[HNO_3]$, 0·105.†

t	12	23	38	51	67	86	120
$[HNO_3]$	0·0565	0·0878	0·0987	0·0995	0·0978	0·0957	0·0905

† Probably slightly low owing to slow equilibration (compare Expt. 37).

TABLE 6. *Molarity of free* HNO_3 *obtained from urea nitrate* (0·2M) *in sulphuric acid–water mixtures at* 25° ± 0·2°.

Expt. 35. H_2SO_4, 91·46% w/w. Equil. val.: $[HNO_3]$ 0·135.

t	10	20	30	41	56	71
$[HNO_3]$	0·1325	0·1293	0·1262	0·1234	0·1190	0·1152

Expt. 36. H_2SO_4, 87·26% w/w. Equil. val.: $[HNO_3]$ 0·091.

t	12	24	35	46	56	75
$[HNO_3]$	0·0888	0·0857	0·0836	0·0815	0·0791	0·0751

Expt. 37. H_2SO_4, 83·64% w/w. Equil. val.: $[HNO_3]$, 0·111.†

t	12	23	36	51	65	77	90	120
HNO_3	0·1370	0·1203	0·1115	0·1066	0·1041	0·1021	0·1008	0·0975

† Probably slightly high owing to slow equilibration (compare Expt. 34).

TABLE 7. *Molarity of free* HNO_3 *from "P.C.X."* (0·2/3M) *in sulphuric acid–water mixtures at* 25° ± 0·2°.

Expt. 38. H_2SO_4, 99·68% w/w. Equil. val.: $[HNO_3]$ 0·165.								
t	18	33	49	62	90	105		
$[HNO_3]$	0·1480	0·1622	0·1650	0·1652	0·1645	0·1654		
Expts. 39, 40.* H_2SO_4, 97·58% w/w. Equil. val.: $[HNO_3]$ 0·129.								
t	16 *	24	33 *	49	49 *	64	76 *	83
$[HNO_3]$	0·1153	0·1220	0·1260	0·1287	0·1292	0·1292	0·1271	0·1287
t	94 *	107 *						
$[HNO_3]$	0·1295	0·1283						
Expt. 41. H_2SO_4, 94·70% w/w. Equil. val.: $[HNO_3]$ 0·090.								
t	15	26	37	52	74	107	191	
$[HNO_3]$	0·0891	0·0882	0·0877	0·0872	0·0844	0·0812	0·0761	
Extp. 42. H_2SO_4, 91·46% w/w. Equil. val.: $[HNO_3]$ 0·065.								
t	18	30	55	73	92	115		
$[HNO_3]$	0·0642	0·0624	0·0620	0·0608	0·0590	0·0584		
Expt. 43. H_2SO_4, 88·46% w/w. Equil. val.: $[HNO_3]$ 0·055.								
t	17	35	47	68	98	131		
$[HNO_3]$	0·0541	0·0507	0·0493	0·0476	0·0433	0·0415		
Expts. 44, 45.* H_2SO_4, 87·26% w/w. Equil. val.: $[HNO_3]$ 0·055.								
t	11 *	15	28	44	60	89	110 *	140 *
$[HNO_3]$	0·0566	0·0548	0·0518	0·0499	0·0479	0·0453	0·0431	0·0356
Expt. 46. H_2SO_4, 85·78% w/w. Equil. val.: $[HNO_3]$ 0·059.								
t	13	26	41	62	87	120		
$[HNO_3]$	0·0600	0·0564	0·0537	0·0516	0·0494	0·0467		
Expt. 47. H_2SO_4, 83·64% w/w. Equil. val.: $[HNO_3]$ 0·065.								
t	11	21	36	53	72	102	129	
$[HNO_3]$	0·0645	0·0627	0·0613	0·0591	0·0576	0·0547	0·0517	
Expt. 48. H_2SO_4, 79·88 w/w. Equil. val.: $[HNO_3]$ 0·066.								
t	13	25	39	52	67	97		
$[HNO_3]$	0·0657	0·0652	0·0648	0·0648	0·0634	0·0622		
Expt. 49. H_2SO_4, 75·38% w/w. Equil. val.: $[HNO_3]$ 0·066 (*t* 14 to 64).								

TABLE 8. *Molarity of free* HNO_3 *obtained from cyclonite* (0·2/3M) *in sulphuric acid–water mixtures at* 25° ± 0·2°.

Expt. 50. H_2SO_4, 99·68% w/w. Equil. val.: $[HNO_3]$ 0·162.								
t	20	30	42	53	65	154		
$[HNO_3]$	0·1533	0·1590	0·1624	0·1617	0·1614	0·1615		
Expts. 51, 52.* H_2SO_4, 97·58% w/w. Equil. val.: $[HNO_3]$ 0·127.								
t	18	26 *	28	37 *	38	49 *	49	62
$[HNO_3]$	0·1128	0·1178	0·1201	0·1239	0·1239	0·1254	0·1260	0·1273
t	81 *	90	92 *	122 *				
$[HNO_3]$	0·1274	0·1264	0·1264	0·1273				
Expt. 53. H_2SO_4, 94·70% w/w. Equil. val.: $[HNO_3]$ 0·088.								
t	41	64	94	125	153	188	261	
$[HNO_3]$	0·0837	0·0812	0·0781	0·0751	0·0724	0·0720	0·0598	
Expt. 54. H_2SO_4, 91·46% w/w. Equil. val.: $[HNO_3]$ 0·053.†								
t	43	57	66	110	159	197	223	
$[HNO_3]$	0·0511	0·0499	0·0496	0·0450	0·0455	0·0428	0·0411	

† Value doubtful, owing to slowness of dissolution.

the method of Walker and Aston (*J.*, 1895, **67**, 576), and found **77**, **100**, and **99** for the percentage of hydrolysis of, respectively, urea, urethane, and *N*-methylurethane hydrochlorides. When concentration differences are taken into account, our value for urea hydrochloride is close to

that previously recorded; and it appears that, by this method, the urethanes are at least 40 times weaker bases than urea.

Ultra-violet Spectra.—Carefully purified urea, urethane, or *N*-methylurethane showed no significant absorption ($\varepsilon < 0{\cdot}5$; *i.e.*, log ε is negative) when dissolved in water, 1·0M-sulphuric acid, or "AnalaR" concentrated (98%) sulphuric acid, and examined over the range 230—400 mμ. The extinction coefficient rose in the region 230—200 mμ, but no differentiation between solutions in water and acid was possible.

Cryoscopic Measurements (By C. HOLSTEAD *and* P. A. H. WYATT).—In an attempt to detect differences in the degree of ionisation of urea and the urethanes in sulphuric acid solutions, cryoscopic measurements were carried out in both sulphuric acid and its monohydrate. The general method of Gillespie, Hughes, and Ingold (*J.*, 1950, 2473) was followed throughout, but with a form of cell similar to that of Newman, Ruivila, and Garrett (*J. Amer. Chem. Soc.*, 1945, **67**, 704), incorporating a Beckmann thermometer and a mechanical stirrer. It was possible to repeat measurements to within about 0·002° when the conditions of supercooling and bath temperature were rigidly adhered to, provided that a damp cloth was wrapped around the upper parts of the apparatus as a protection against changes of laboratory temperature which could otherwise produce large errors.

(a) *Sulphuric acid as solvent.*

Expt. (i). Urea as solute: molality of added water 0·060.						
Molality of urea	(m)	0·01933	0·03937	0·06003	0·08202	0·1068
Depression	(θ)	0·227°	0·468°	0·719°	0·987°	1·296°
No. of ions	(ν)	2·02	2·06	2·06	2·08	2·09
„ „	(ν')	1·96	1·98	2·00	2·00	2·02
Expt. (ii). Urea as solute: molality of added water 0·062.						
	m	0·02271	0·04431	0·06874	0·09541	0·1214
	θ	0·269	0·527	0·821	1·154	1·487
	ν	2·04	2·04	2·05	2·08	2·11
	ν'	1·98	1·98	1·99	2·02	2·04
Expt. (iii). Urethane as solute: molality of added water 0·064.						
	m	0·01067	0·03331	0·05722	0·08046	0·1078
	θ	0·129	0·404	0·708	0·994	1·343
	ν	2·07	2·08	2·11	2·11	2·14
	ν'	2·02	2·02	2·06	2·06	2·08
Expt. (iv). Urethane as solute: molality of added water 0·055.						
	m	0·02545	0·05053	0·07513	0·09991	0·1253
	θ	0·302	0·605	0·905	1·219	1·551
	ν	2·04	2·04	2·06	2·08	2·12
	ν'	1·98	2·00	2·01	2·03	2·06
Expt. (v). *N*-Methylurethane as solute: molality of added water 0·066.						
	m	0·009031	0·02748	0·04776	0·06829	0·09035
	θ	0·109	0·336	0·589	0·847	1·140
	ν	2·06	2·09	2·12	2·12	2·16
	ν'	2·01	2·03	2·05	2·07	2·10

(b) *Sulphuric acid monohydrate as solvent.*

Expt. (vi). Urea as solute.						
	m	0·05495	0·1208	0·1857	0·2451	0·2898
	θ	0·226	0·520	0·853	1·214	1·495
Expt. (vii). Urethane as solute.						
	m	0·06122	0·1132	0·1642	0·2165	0·2673
	θ	0·247	0·497	0·747	1·055	1·399
Expt. (viii). Nitromethane as solute.						
	m	0·1108	0·1669	0·2494	0·3308	
	θ	0·435	0·625	0·942	1·270	

Sulphuric acid monohydrate required two slight alterations in technique: the best degree of supercooling was found to be 1·8° (instead of 1·5°), and seeding was necessary as crystallisation could not be induced by solid carbon dioxide. The results are tabulated above. All depressions are corrected for supercooling by using the factors 0·012 (H_2SO_4) and 0·011 (H_2SO_4,H_2O). When additional water is present, θ refers to the depression of the f. p. below that of the treated solvent.

The ν values recorded in experiments (i)—(v) have been calculated in the same way as

those of Gillespie, Hughes, and Ingold (*loc. cit.*), with the assumption that no solvation occurs. It would be possible to bring all the values much nearer 2·00 by introducing other solvation assumptions, but since the basis of these calculations is open to objections (Wyatt, *J.*, 1953, 1175), no further elaboration of this kind is presented here, especially as the immediate object was to detect differences in behaviour between urea and the urethanes. The values obtained from the empirical expression $\nu' = \theta/6{\cdot}0m$ (*loc. cit.*) are, however, included. The figures clearly show that there can be no significant difference in the degree of ionisation of urea, urethane, and *N*-methylurethane, all of which are probably completely monoprotonated in 100% sulphuric acid.

In sulphuric acid monohydrate also urea and urethane show identical behaviour up to 0·22M, as can easily be demonstrated by plotting the data of experiments (vi) and (vii) on the same graph. The sensitivity of this test is, however, somewhat less than for 100% sulphuric acid, since the depression for a bisulphate which gives two ions in this solvent is only about 33% greater than for a non-electrolyte at 0·25M, because of the large concentration of HSO_4^- ions in the solvent. Nevertheless, at concentrations (>0·22M) sufficient for a difference to appear between urea and urethane, it is such as to make urethane appear a stronger base than urea. Since urea is almost certainly monoprotonated at this concentration of sulphuric acid, it is concluded that urethane cannot be un-ionized to any extent detectable by this method.

Nitromethane has been found to be a very satisfactory non-electrolyte for comparison in this work. The data of Expt. (viii), when recalculated on a mol.-fraction basis (as is most convenient for the concentrated solutions involved) and plotted on a graph of θ against $-(1-0{\cdot}0013\ \theta)\ \log_{10}N_1$, yield a slope of 77·0, which is equivalent to a conventional cryoscopic constant of 3·88° g.-mol.$^{-1}$ kg. This is in satisfactory agreement with the value 3·95° calculated from Rubin's calorimetric data (Yost and Russell, "Systematic Inorganic Chemistry," Prentice-Hall, New York, 1944, p. 337).

THE UNIVERSITY, SHEFFIELD, 10. [*Received, April 11th*, 1953.]

672. *Nitramines and Nitramides. Part VI.* Some N-Nitrations in Solvents Other than Sulphuric Acid.*

By C. HOLSTEAD and ALEX. H. LAMBERTON.

In contrast with the behaviour in sulphuric acid, the nitrations of urethane, *N*-methylurethane, and urea are not reversible in acetic anhydride–acetic acid. Urethane is not nitrated in acetic acid as solvent. The nitrations of urethane and of guanidine are reversible in 60% perchloric acid, or in selenic acid.

WHEN urethane, *N*-methylurethane, or urea was allowed to react with one molecular proportion of nitric acid in, essentially, acetic anhydride (Ac_2O : AcOH = 96 : 4, w/w) the concentration of free nitric acid fell, but did not tend towards an equilibrium value. No nitric acid was set free when the corresponding nitramides were dissolved in the same solvent. The indicated yields in the nitration process were good (60—80% after one hr. at 25°). Urethane and urea were nitrated at similar speeds, but *N*-methylurethane was nitrated more rapidly. More precise conclusions seem unwise: we measured the concentration of nitric acid, and this may be reduced by reactions other than the nitration of the amides. The reaction between nitric acid and acetic anhydride is the most obvious of these, though probably of little significance in the time available. It was qualitatively possible to isolate the nitramides, and we believe that the yields quoted in this, and the next, paragraph are accurate to within 5%. A fuller discussion is postponed to the Experimental section.

The nitration of urethane has also been investigated in other acetic anhydride–acetic acid mixtures, and in acetic acid alone. In mixtures containing acetic anhydride (Ac_2O : AcOH = 50 : 50, w/w; and Ac_2O : AcOH = 5 : 95, w/w) nitration took place, though more slowly: the indicated yields were 80 and 40%, respectively, after 20 hours at 25°. In acetic acid (AcOH : H_2O = 99·5 : 0·5, w/w) no nitration could be detected. It appears that some acetic anhydride (or, possibly, the absence of water) is necessary; and

* Part V, preceding paper.

the non-reversibility of the reaction indicates clearly why most workers have empirically preferred acetic anhydride to sulphuric acid as a solvent medium for *N*-nitration.

The nitrations of urethane and guanidine have been found to be reversible in 60% perchloric acid; the processes were slower than in concentrated sulphuric acid, but, by working at 70°, urethane and guanidine were brought to equilibrium with the corresponding *N*-nitro-compounds in, respectively, 20 minutes and 10 hours. The yields indicated were *ca.* 53% of nitrourethane and *ca.* 21% of nitroguanidine. Irreversible decomposition could be detected after prolonged heating at 70°, but did not appear to be significant in periods of up to an hour for nitrourethane, or 15 hours for nitroguanidine; the same equilibrium values were obtained by the use of nitrourethane and nitroguanidine as initial materials.

The behaviour of selenic acid as a solvent has been investigated briefly. Addition of nitrourethane or nitroguanidine to acetanilide in selenic acid (91·0%, w/w) gave *p*-nitroacetanilide in yields comparable with those previously obtained (Part III, *J.*, 1952, 1886) by the use of sulphuric acid.

It was found impossible to make a 0·2M-solution of guanidine nitrate in acetic anhydride–acetic acid (96 : 4, w/w), and guanidine nitrate was precipitated when nitric acid was added at 25° to a solution made up from guanidine carbonate and the solvent. The nitration of guanidine in acetic anhydride could not, therefore, be compared quantitatively with that of the urethanes or of urea.

Experimental

The solutions were made up, and analysed for free nitric acid in the presence of *N*-nitro-compounds, in the manner previously described (Part V, *loc. cit.*; Simkins and Williams, *J.*, 1952, 3086). When required, nitric acid (70%, w/w) was added immediately before the introduction of the amide, and the solvent compositions reported take into account the water thus added. Blank trials, and standardisation by means of potassium nitrate, showed that neither acetic nor perchloric acid affected the determination of nitric acid.

Table 1. *Fall in nitric acid, initially* 0·2M *in acetic anhydride–acetic acid media. caused by urethane, N-methylurethane, or urea*

Initial amide concn., 0·2M. Temp. 25° ± 0·2°.‡ Times are in minutes.

Expt. 1. Urethane and nitric acid in Ac_2O : AcOH = 96 : 4, w/w.

t	10	22	37	57	90	126	169	270	375
$[HNO_3]$ ...	0·1463	0·1177	0·0977	0·0843	0·0710	0·0629	0·0549	0·0472	0·0417

Expt. 2. *N*-Methylurethane and nitric acid in Ac_2O : AcOH = 96 : 4, w/w.

t	11	22	39	60	93	150	250	357
$[HNO_3]$ ...	0·0719	0·0563	0·0464	0·0394	0·0330	0·0273	0·0224	0·0196

Expt. 3. Urea and nitric acid in Ac_2O : AcOH = 96 : 4, w/w.

t	10	22	39	61	91	150	256	383
$[HNO_3]$ ...	0·1730	0·1377	0·1088	0·0852	0·0684†	0·0517†	0·0396†	0·0331†

Expt. 4. Urethane and nitric acid in Ac_2O : AcOH = 50 : 50, w/w.

t	10	28	59	120	270	450	702	1338
$[HNO_3]$ ...	0·1750	0·1484	0·1237	0·0990	0·0739	0·0608	0·0503	0·0390

Expts. 5, 6. Urethane and nitric acid in Ac_2O : AcOH = 5 : 95, w/w.

t (Expt. 5)	11	26	65	150	267	395	1123
$[HNO_3]$ ...	0·1973	0·1955	0·1896	0·1800	0·1685	0·1584	0·1247
t (Expt. 6)	731	1470	2171	2959	3765	5435	
$[HNO_3]$ ...	0·1396	0·1154	0·1020†	0·0914†	0·0839†	0·0727†	

† These values are probably lower than would be the case if HNO_3 were removed solely by nitration of the amide. Values so marked correspond to the loss of 5% (or more) of HNO_3 from solutions of HNO_3 (0·2M) and the nitramide (0·2M) in the same solvent : it has been assumed that the solvent of Expt. 4 would behave like that of Expt. 5.

‡ Room temperature (*ca.* 20°, uncontrolled) during initial mixing (3 min.).

Nitration of the Urethanes in Acetic Anhydride–Acetic Acid Media.—The decreases in nitric acid concentration are given in Table 1; they do not necessarily indicate the extent of nitration. First, nitric acid may be removed by reaction with acetic anhydride. A blank experiment, in

the absence of urethane, showed that the concentration of nitric acid in acetic anhydride (Ac_2O : AcOH = 96 : 4, w/w) fell only from 0·2000 to 0·1950M in 6 hr. at 25°. In the actual experiments the concentration of nitric acid was, for most of the time, less than 0·1M, and therefore the loss from this source was presumably smaller than that observed in the blank. We have assumed that the reaction would not be significant in the media containing 50 or 95% of acetic acid, and consider that losses from this source do not lead to a significant over-estimation of the degree of nitration.

Secondly, the residual nitric acid may react with the nitramide (or decomposition products thereof). We were unable, through bluntness of the end-point, to determine the total nitric acid (free and available from $>N{\cdot}NO_2$) by electrometric titration of samples dissolved in an excess of concentrated sulphuric acid. Instead, solutions were made up containing the nitramide (0·2M) and nitric acid (0·2M): the losses from these solutions were presumably greater than those in the main experiments, where both solutes were present in lower concentration. In acetic anhydride (Ac_2O : AcOH = 95 : 4, w/w) the concentration of nitric acid in the presence of nitrourethane fell from 0·2000 to 0·1943M in 6 hr. at 25°, a loss similar to that observed in the absence of nitrourethane. We have assumed that the loss would be no greater in the presence of *N*-methylnitrourethane, which is known to be more stable to acid reagents.

On the other hand, a loss (0·2000 to 0·1989, 0·1937, 0·1852, 0·1773, and 0·1699M in, respectively, 0·8, 17·1, 42·4, 68·2, and 90·0 hr. at 25°) was found when nitric acid was kept, in the presence of nitrourethane, in acetic acid containing a little anhydride (Ac_2O : AcOH = 5 : 95, w/w). We do not suggest that these losses were due to the change from the anhydride to the acid: in the predominantly acid medium the time involved was much greater. Nitration, however, was slow in the acid (Ac_2O : AcOH = 5 : 95, w/w) medium, and it seems likely that after, say, 25 hr. the (observed) fall in nitric acid may be significantly greater than that due to nitration alone.

Nitration of Urea in Acetic Anhydride–Acetic Acid (96 : 4, w/w).—The fall in nitric acid concentration is given in Table 1; it is subject to the same limitations as that discussed above. The loss of nitric acid from a solution (initially 0·2M in nitric acid and in nitrourea) in acetic anhydride (Ac_2O : AcOH = 96 : 4, w/w) was comparatively rapid: the residual free nitric acid was 0·1947, 0·1868, 0·1683, 0·1625, 0·1479, and 0·1428M after, respectively, 21, 76, 214, 270, 344, and 378 min. at 25°. It thus appears that in the case of urea in acetic anhydride (Ac_2O : AcOH = 96 : 4, w/w), the reduction in nitric acid may be significantly greater (after the first hour) than that due to nitration alone. It can be seen, from Table 1, that the observed fall in nitric acid was initially greater in the presence of urethane, but finally greater in the presence of urea. We consider this to be due simply to the more rapid removal of nitric acid by nitrourea (or its decomposition products).

Irreversibility of Nitration in Acetic Anhydride.—0·2M-Solutions of nitrourethane, *N*-methylnitrourethane, or nitrourea in acetic anhydride (Ac_2O : AcOH = 96 : 4, w/w) were kept at 25°, and yielded no free nitric acid (within experimental error) in periods of up to 6 hr. (Maximum [HNO_3] found, 0·0006M.)

Absence of Nitration in Acetic Acid Alone.—A solution of urethane (0·2M) and nitric acid (0·2M) in acetic acid (AcOH : H_2O = 99·5 : 0·5, w/w) was kept at 25°, and showed no fall in free nitric acid (within experimental error) in periods of up to 18 hr. (Minimum [HNO_3] found, 0·1995M.)

Qualitative Isolation of the Nitramides.—(*a*) Urea nitrate (10 g.) was added to acetic anhydride–acetic acid (30 : 5 ml.) at 60°. After 35 min. at 60° the solution was cooled in ice, and crude nitrourea (2·5 g.; m. p. 143°, decomp.) collected. Two crystallisations from alcohol yielded pure material, identified by mixed m. p. and formation of the *S*-benzylthiuronium salt. (*b*) Urethane (13·5 g.) was added portionwise, below 25°, to a mixture of acetic anhydride (30 ml.) and nitric acid (11 ml. of 98%). After 1 hr. at 20—25°, the solution was poured into water, and extracted with ether, and the extract washed once with water. Part of the washed extract was dried and evaporated (finally *in vacuo* over KOH) to yield nitrourethane, m. p. 59—63°; the remainder was treated with gaseous ammonia to precipitate salts, from which pure ammonium nitrourethane could be obtained by one crystallisation from alcohol. (*c*) The preparation of *N*-methylnitrourethane in good yield in an acetic anhydride medium has been reported by Curry and Mason (*J. Amer. Chem. Soc.*, 1951, **73**, 5043).

Experiments in Perchloric Acid.—The results are given in Table 2. Equilibrium values were obtained, as explained in Part V (*loc. cit.*), by extrapolation back to zero time: since little irreversible decomposition was apparent in the course of the experiments, these values do not differ greatly from the final (observed) concentration of nitric acid. The sampling pipette was calibrated (by weight delivered) in terms of molarity at 25°, and the molarity of nitric

acid reported is thus that which would have occurred in the solution after sudden cooling, without chemical change, to 25°. Owing to thermal expansion, the true molarities at 70° must have been somewhat smaller.

TABLE 2. *Reversible nitrations of urethane and guanidine in* 60% *perchloric acid at at* 70° ± 0·2°.

Molarity of HNO_3 in terms of solutions at 25°; times are in minutes.

Expt. 7. Urethane and nitric acid (both 0·2M at 25°) in perchloric acid (60·1%, w/w). Equil. val.: $[HNO_3]$, 0·094M.

t	8	16	27	41	55	75
$[HNO_3]$	0·1189	0·0953	0·0930	0·0928	0·0920	0·0907

Expt. 8. Nitrourethane (0·2M at 25°) in perchloric acid (60·8%, w/w). Equil. val.: $[HNO_3]$, 0·095M.

t	6	16	26	36	60	77
$[HNO_3]$	0·0558	0·0926	0·0941	0·0940	0·0919	0·0894

Expts. 9, 10.* Guanidine nitrate (0·2M at 25°) in perchloric acid (60·8%, w/w). Equil. val.: $[HNO_3]$, 0·158M

t	18	30	60	96	150	240
$[HNO_3]$	0·1872	0·1823	0·1780	0·1724	0·1653	0·1604
t	360	540	710*	840*	1100*	
$[HNO_3]$	0·1582	0·1578	0·1573	0·1572	0·1563	

Expts. 11, 12.* Nitroguanidine (0·2M at 25°) in perchloric acid (60·8%, w/w). Equil. val.: $[HNO_3]$, 0·158M.

t	9	21	36	58	88	143
$[HNO_3]$	0·0073	0·0173	0·0308	0·0467	0·0674	0·0972
t	215	320	566	736*	916*	1083*
$[HNO_3]$	0·1217	0·1423	0·1548	0·1573	0·1570	0·1564

* Asterisks relate values of t to experiment numbers similarly marked.

Nitration of Acetanilide by Means of Nitrourethane or Nitroguanidine in Selenic Acid.—Nitrourethane or nitroguanidine (2·5 m.-mol.) was added during 20 min. at 25° to a stirred solution of acetanilide (2·5 m.-mol.) in selenic acid (2·5 ml. of 91·0%, w/w). After 20 min. at 25°, the solution was poured on ice (35 g.) to yield *p*-nitroacetanilide, m. p. 211°. The yield from nitrourethane was 74%; from nitroguanidine, 50%; from potassium nitrate (control), 75%.

THE UNIVERSITY, SHEFFIELD, 10.

Received April 11th, 1953.]

---

673. *The Mechanism of Hydrolysis of Acid Chlorides. Part V.* The Effect of Solvent and Hydroxyl Ions on the Rate of Solvolysis of Substituted Benzoyl Chlorides.*

By D. A. BROWN and R. F. HUDSON.

Studies of the effect of solvent composition and added hydroxide ions on the rate of hydrolysis of substituted benzoyl chlorides show that a change in mechanism from S_N2 to S_N1 occurs in the following order:

$(S_N2) - 2:4:6\text{-}(NO_2)_3 \simeq p\text{-}NO_2 > H > p\text{-}CH_3O \gg 2:4:6\text{-}(CH_3)_3 - (S_N1)$

The nature of solvation of the transition state in aqueous mixtures is discussed, and the change in rate of S_N1 solvolysis with changes in solvent composition is attributed entirely to changes in entropy of solvation.

The observed increases in activation energy with water content are shown to be due to the gradually changing structure of the transition state, and not directly to changes in the structure of the solvent.

PREVIOUS papers have dealt with the effect of substitution on the rate of hydrolysis of benzoyl chloride in media of low and high water content, and the considerable change in rate order has been discussed in terms of a gradual change in mechanism from a bimolecular

* Part IV, *J.*, 1953, 888.

(S_N2) to a unimolecular ionisation process (S_N1). The effect of increasing the water content of the medium on the rate of hydrolysis in the case of the unsubstituted chloride at various temperatures is in agreement with this interpretation, for a considerable increase in activation energy is observed.

To broaden the investigations, it was decided to investigate the variations in E and k with changes in solvent composition for several substituted chlorides containing strong electron-donating and electron-attracting groups and to compare the effects with the corresponding behaviour of well-established S_N1 reactions.

Experimental

Purification of Materials.—Acetone, benzoyl chloride and *p*-nitrobenzoyl chloride were all purified as described by Hudson and Wardill (*J.*, 1950, 1729). *p*-Methoxybenzoyl chloride was purified by distillation twice under reduced pressure; it had b. p. 145°/14 mm. 2 : 4 : 6-Trinitrobenzoyl chloride was prepared from 2 : 4 : 6-trinitrobenzoic acid by means of thionyl chloride, and purified by repeated recrystallisation from light petroleum; it had m. p. 158°.

2 : 4 : 6-Trimethylbenzoyl chloride was prepared from mesitylene by bromination, conversion of the product into the acid *via* the Grignard reagent by means of carbon dioxide, and treatment of the acid as usual; the chloride was purified by distillation under reduced pressure, and then had b. p. 118°/18 mm. 2 : 4 : 6-Trimethylbenzyl chloride was prepared by treating mesitylene with formaldehyde and concentrated hydrochloric acid, and similarly purified; it had b. p. 130°/22 mm., m. p. 37°.

Table 1. *Effect of* OH^- *on the solvolysis of* p-*methoxybenzoyl chloride.*

Solvent composition: 75% aqueous acetone by volume. Temperature of reaction medium: 0·2°. Initial concn. of chloride (*a*): 2·424 × 10^{-3} mole/l. Initial concn. of NaOH (*b*): 5·790 × 10^{-3} mole/l. Mean k_2 = 0·40(4) ± 0·015 l. mole^{-1} sec.$^{-1}$.

Time, secs.	No. of drops of HCl	Reaction, %	10^3x, mole/l.	$10^3(a-x)$, mole/l.	$10^3(b-2x)$, mole/l.	k_2
69	4	14·0	0·3402	2·084	5·109	0·350
79	5	17·5	0·4253	1·999	4·939	0·405
96	6	21·1	0·5103	1·914	4·769	0·417
132	7	24·6	0·5954	1·829	4·699	0·460
150	9	29·8	0·7654	1·659	4·259	0·397
196	10	35·1	0·8505	1·574	4·089	0·396
256	12	42·1	1·021	1·403	3·749	0·402
369	15	52·6	1·276	1·148	3·238	0·410
541	18	63·2	1·530	0·8937	2·729	0·406
705	20	70·2	1·701	0·7230	2·388	0·398
925	22	77·2	1·871	0·5530	2·048	0·409

Table 2. *The effect of solvent and temperature on the rate of hydrolysis of benzoyl chloride in dioxan–water mixtures.*

Temp.	% H_2O (v/v)	N_{H_2O} †	Concn. of chloride, mole l.$^{-1}$	10^5k_1, sec.$^{-1}$	10^5k_1, mean
15°	5 *	—	0·0217	3·81	3·90
			0·0201	3·98	
25	,,	0·2000	0·0253	7·80	7·71
35	,,	—	0·0217	7·62	14·8
			0·0285	14·61	
			0·0276	14·98	
15	10 *	—	0·0208	10·51	10·60
			0·0219	10·69	
25	,,	0·3520	0·0250	21·19	21·40
			0·0261	21·61	
35	,,	—	0·0201	41·81	41·80
			0·0215	41·79	
15	15	—	0·0289	17·01	17·10
			0·0297	17·19	
25°	15	0·4630	—	—	36·8 ‡
35	,,	—	—	—	77·4 ‡
15	20	—	0·0271	24·13	24·27
15	,,	0·5500	0·0280	24·41	
25	,,	—	—	—	56·0 ‡
35	—	—	—	—	122·0 ‡
15	33⅓	—	0·0219	60·01	60·1
			0·0206	60·19	
25	,,	0·7096	—	—	144·0 ‡
35	,,	—	—	—	323·0 ‡
15	50	0·8301	0·0256	261·2	260·6
25	,,	—	0·0217	260·0	
			—	—	>600·0 ‡

* Results obtained by acidimetric titration method. † N_{H_2O} = mole-fraction of H_2O.
‡ These rate values were obtained by J. Wardill.

Rate Measurement.—Three different methods were employed, depending on the rate of the reaction and the accuracy required. The experiments with benzoyl chloride in water–dioxan mixtures utilised the conductivity method described by Archer and Hudson (*J.*, 1950, 3259)

since the activation energies were required with the maximum accuracy. In most cases, the rate was followed electrometrically by the balancing-cell method used by Hudson and Wardill (*loc. cit.*). The method was improved by the following modifications. Only a small volume (5 ml.) of acetone was used as solvent for the chloride before initiating the reaction, because it was found that the addition of this amount to the acetone–water mixture at the same temperature produced no appreciable temperature change in the resulting reaction medium. The concentration of acid liberated on completion of reaction was measured either by direct balancing of the reaction and titration cells, or by volumetric and/or gravimetric analysis. In all experiments the temperature of the reaction mixture was measured by means of a calibrated " thermistor " resistance, in order to detect very small temperature changes.

Reaction with 2 : 4 : 6-trinitrobenzoyl chloride was so slow that the rate was followed by titration of liberated hydrogen chloride after removal of the unhydrolysed chloride by ether-extraction (Olivier and Berger, *Rec. Trav. chim.*, **1926**, **45**, 452). Direct titration of the mixture in acetone, with lacmoid as indicator, which was used for following the rate of hydrolysis of 2 : 4 : 6-trimethylbenzyl chloride, could not be employed for the trinitrobenzoyl chloride because sodium hydroxide reacts with 2 : 4 : 6-trinitrobenzoic acid non-stoicheiometrically.

Evaluation of Rate Constants.—Except in the experiments in alkaline solution, the rate constant k_1 was evaluated graphically by applying the first-order rate equation. In the presence of hydroxide ions, the rate is given by $dx/dt = k_1(a - x) + k_2(a - x)(b - 2x)$, where a and b are the initial concentrations of chloride and hydroxide respectively. Integration leads to the general equation

$$t[k_1 + k_2(b - 2a)] = \ln[a/(a - x)] - \ln\{(k_1 + k_2b)/[k_1 + k_2(b - 2x)]\}$$

As the value of k_1 is known from the neutral hydrolysis, the bimolecular rate constant for the hydroxide reaction k_2 may be obtained by successive approximations. This yields more accurate values than the graphical determination of the initial rate previously employed (Hudson and Wardill, *loc. cit.*), and the results of a typical experiment are given in Table 1.

Discussion

An ionisation reaction (S_N1) is characterised by (*a*) the lack of bond formation between two dissimilar molecules and (*b*) considerable separation of charge in one particular bond only. Consequently, the transition states in these reactions are similar in structure, and it is not surprising, therefore, that the rates of solvolysis are related uniformly to the solvating power of the solvent (Grunwald and Winstein, *J. Amer. Chem. Soc.*, **1948**, **70**, 846). This mechanism in general is associated with high activation energies, which are found to be approximately constant for several alkyl halides in alcohol, water, and mixed solvents. The considerable changes in velocity constant with solvent are therefore due almost entirely to changes in the collision frequency.

Similarly the heats of solvation of salts in water and the alcohols are very similar (Mischenko, *Acta Physicochim. U.R.S.S.*, **1935**, **3**, 693). The free energy of solvation changes considerably with the polarity of solvent, so that ion solvation is controlled mainly by the entropy change. The similarity of salt ionisation and S_N1 solvolysis is shown by the following comparison. The difference in ΔF of solvation of KCl and NaCl in water and methyl alcohol is approximately 7·5 cal./mole (Latimer and Slansky, *J. Amer. Chem. Soc.*, **1940**, **62**, 2020). This would account for a rate ratio of *ca.* 10^5 compared with the observed value of $0{\cdot}4 \times 10^5$ for the solvolysis of *tert.*-butyl chloride (Olsen and Halford, *ibid.*, **1937**, **59**, 2644). It seems highly probable, therefore, that the change in velocity of an S_N1 reaction may be attributed almost entirely to changes in entropy of solvation.

Consider a similar reaction which is proceeding by a bimolecular S_N2 mechanism: the influence of the nucleophilic reagent A is to decrease the activation energy by partial bond formation, and by reduced extension of R–X: $A + R{-}X \longrightarrow A{-}R{-}X$. For a given increase in the polarity of the solvent, the change in $-\Delta F_s$ will be greater for the ionisation process than for the S_N2 process, the charge distribution being assumed to be smaller and less localised in the latter case, irrespective of the nature of the solvent forces (see below). This condition is expressed in Hughes and Ingold's generalisation that solvation influences S_N1 to a greater extent than S_N2 reactions (*J.*, **1935**, 244).

The greater value of $-\Delta F_s$ tends to promote the S_N1 mechanism, involving a decrease in the energy contribution from the partially formed bond, with a consequent increase in

E^*. Simultaneously, the contribution to the entropy decrease due to the interaction of the attacking molecule and the central carbon atom is reduced, so that the resultant increase in activation entropy is due to two inter-related effects. According to this view, the increases in E with solvent polarity are caused by changes in transition-state structure, and not by changes in the structure of the solvent only. These energy changes have been attributed to the increased force necessary to remove a solvent molecule from the pseudo-crystalline structure of the more polar liquid (Pearson, *J. Chem. Phys.*, **1952**, **20**, 1478). Clearly, this effect would be greater in S_N1 reactions, which are controlled entirely by solvent action, *i.e.*, in cases where the actual changes in E^* are negligible.

The experimental activation energies given in Tables 3 and 4, and related to water content in Fig. 1, show that the change is less in the hydrolysis of *p*-methoxybenzoyl chloride, which tends to react by the S_N1 mechanism, than in that of the corresponding nitro-compound. The presence of a strongly electron-attracting group in the latter promotes the S_N2 mechanism, so that a considerable change in transition-state structure is produced by increasing the ionising power of the medium in order to promote the S_N1 mechanism.

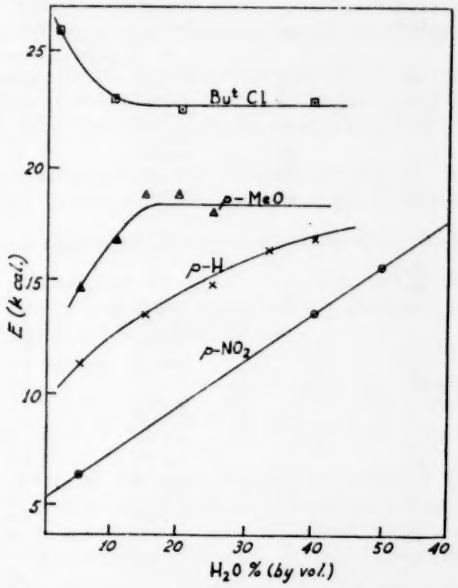


FIG. 1.
Benzoyl chlorides in acetone–water.
tert.-Butyl chloride in methanol–water.

TABLE 3. *The effect of solvent on Arrhenius parameters for the hydrolysis of benzoyl chloride.*

% Water (v/v)	N_{H_2O}	10^5k_1, sec.$^{-1}$	E_{15-25}	log P_{25}	E_{25-35}	log P_{35}
5	0·2000	7·71	11·6	4·387	11·9	4·613
10	0·3520	21·40	12·0	5·132	12·2	5·278
15	0·4630	36·8	13·1	6·176	13·6	6·539
20	0·5500	56·0	14·3	7·238	14·2	7·166
33⅓	0·7096	144·0	14·9	8·088	14·8	8·109
50	0·8301	>600	—	—	—	—

The Nature of the Solvation.—The energy and entropy changes of reactions leading to pseudo-ionic transition states have recently been interpreted by Pearson (*loc. cit.*) in terms of Kirkwood's theory of dipole interaction (*J. Chem. Phys.*, **1934**, **2**, 351). According to this treatment, which assumes a Born changing process, the free energy of a dipole of moment μ and radius r in a liquid of dielectric constant D is given by

$$-\Delta F = kT \ln x = \mu^2(D - 1)/r^3(2D + 1)$$

TABLE 4. *The effect of solvent on the rate of hydrolysis of substituted benzoyl chlorides.*

Temp.	% H_2O (v/v)	Concn. of chloride	10^4k_1, sec.$^{-1}$	10^4k_1, mean	E	log PZ
			p-Nitrobenzoyl chloride.			
0°	5	—	—	5·86 *	—	—
15	,,	—	—	12·3 *	6·67	2·12
25	,,	—	—	16·9 *	—	—
0	15	0·00219	12·55	12·65	,,	,,
,,	,,	0·00258	12·76			
,,	20	0·00228	16·12	16·20	—	—
,,	,,	0·00289	16·28			
,,	25	0·00356	20·50	20·32	—	—
,,	,,	0·00187	20·15			
0	40	0·00371	48·96	50·16	—	—
,,	,,	0·00320	51·37			
— 9·9	,,	0·00251	19·95	—	—	—
—10·1	,,	0·00221	18·84	—	13·7	8·65
—11·7	,,	0·00219	15·90	—	—	—
—15·6	,,	0·00312	10·64	—	—	—
			2 : 4 : 6-Trinitrobenzoyl chloride.			
0	10	0·0115	0·3908	0·4017	—	—
,,	,,	0·0107	0·4127			
20·1	,,	0·0119	2·2776	2·82	15·5	6·81
,,	,,	0·0121	2·865			
0	20	0·0101	0·7711	0·733	—	—
,,	20	0·0120	0·6950			
,,	30	0·0109	0·9826	1·029	—	—
		0·0121	1·075			
			p-Methoxybenzoyl chloride.			
25	5	—	—	0·292 *	14·7	5·89
35	,,	—	—	0·654 *	—	—
0	10	0·0275	0·1271	0·128	16·8	8·56
,,	,,	0·0270	0·1289			
15	,,	0·0281	0·647	0·639	17·7	—
,,	,,	0·0219	0·631			
25	,,	0·0210	1·79	1·80	—	—
,,	,,	0·0320	1·81			
0	15	0·0212	0·415	0·429	18·9	10·77
,,	,,	0·0272	0·443			
15	,,	0·0251	2·62	2·63	—	—
,,	,,	0·0201	2·65			
0	20	0·0195	1·259	1·252	18·9	11·24
,,	,,	0·0310	1·244			
12	,,	0·0197	4·946	4·940	—	—
,,	,,	0·0215	4·933			
0	25	0·00415	2·820	—	—	10·87
— 4·65	,,	0·00519	1·303	—	18·0	—
—12·46	,,	0·00301	0·535	—	—	—
—13·9	,,	0·00356	0·4950	—	—	—
0	30	0·00391	7·12	7·03	—	—
,,	,,	0·00410	6·93			
			2 : 4 : 6-Trimethylbenzoyl chloride.			
0·2	5	0·00195	15·84	—	—	—
— 3·5	,,	0·00221	8·861	—	—	—
— 7·1	,,	0·00250	5·041	—	22·0	14·78
—10·75	,,	0·00181	2·890	—	—	—
— 8·8	10	0·00270	71·29	—	—	—
—10·75	,,	0·00219	50·30	—	—	—
—12·2	10	0·00250	42·18	—	24·0	17·67
—16·1	,,	0·00210	18·84	—	—	—
—19·2	,,	0·00310	10·87	—	—	—
			2 : 4 : 6-Trimethylbenzyl chloride.			
30·0	25	0·0215	0·1308	0·1342	—	—
,,	,,	0·0192	0·1376		—	—
20·4	50	0·0105	105·5	103·2	—	—
—	—	0·0112	101·1		—	—

* Values taken from Part III.

Results in the concentration range 0·01—0·03N were obtained by acidimetric titration method. Results in the 0·002—0·005N concentration range were obtained by the electrometric method.

By differentiation with respect to temperature, an equation for the entropy change is obtained which, combined with the above equation, leads to an expression for the heat of solvation. These expressions may be combined with the general equation of the absolute rate theory

$$k = \left(\frac{kT}{h}\right)e^{-\Delta F/RT} = \left(\frac{kT}{h}\right)e^{\Delta S/R}e^{-\Delta H/RT}$$

to give corresponding relations for heat and entropy of activation :

$$\left[\frac{\partial \Delta F^*}{\partial T}\right] = -\Delta S^* = \frac{3D}{(2D+1)^2}\cdot\left[\frac{\mathrm{d}\ln D}{\mathrm{d}T}\right]_p \cdot \Sigma\frac{\mu^2}{r^3}$$

and

$$-\Delta H = \left[\left(\frac{D-1}{2D+1}\right) + \frac{3DT}{(2D+1)^2}\left(\frac{\mathrm{d}\ln D}{\mathrm{d}T}\right)_p\right]\cdot\Sigma\frac{\mu^2}{r^3}$$

where $\Sigma\frac{\mu^2}{r^3}$ refers to the difference in $\frac{\mu^2}{r^3}$ for reactants and transition state. Assuming a likely value for this factor representing the increase in polarity of the transition state, we reach the following conclusions: (*a*) $(-\Delta F)$ increases regularly with dielectric constant; (*b*) $(-\Delta H)$ is approximately constant for most polar liquids; (*c*) the change in $(-\Delta F)$ is due almost entirely to changes in $(-\Delta S)$.

Conclusions (*b*) and (*c*) are in qualitative agreement with data on the ionisation of salts and solvolysis of alkyl halides already considered, although the magnitude of the calculated values, a likely value for $\Sigma\frac{\mu^2}{r^3}$ being assumed, is much less than experimentally observed in these reactions. In addition, a uniform relation between ΔF and D is not observed in the case of ionisation S_N1 reactions as shown by the following values for the solvolysis of *tert.*-butyl chloride (see values listed by Grunwald and Winstein, *loc. cit.*).

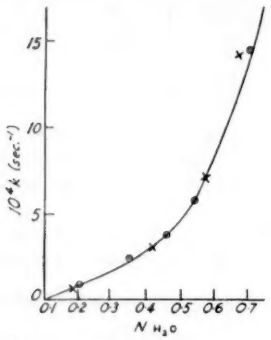
Solvent	D	E	K	Solvent	D	E	K
Acetic acid ...	7·1	26·43	$2{\cdot}1 \times 10^{-7}$	Water	80	22·6	$3{\cdot}3 \times 10^{-3}$
Ethyl alcohol	25	26·0	$9{\cdot}7 \times 10^{-8}$	48·6% H_2O in dioxan	34	22·8	$1{\cdot}81 \times 10^{-4}$
Methyl alcohol	32·5	25·0	$8{\cdot}2 \times 10^{-7}$	80% aqueous acetone (v/v)	33·4	22·6	$1{\cdot}94 \times 10^{-6}$
Formic acid ...	47	22·9	$1{\cdot}1 \times 10^{-3}$				

Owing to the inadequacy of this treatment, the solvation process can probably be treated more satisfactorily, as in the case of the ionisation of salts, by considering an inner solvation shell to be formed by co-ordination of a definite number of solvent molecules surrounded by an outer layer in which solvent molecules are mobile. It is solvation due to the solvent molecules in this outer shell only which can be treated by the above method, and, as shown by Eley and Evans (*Trans. Faraday Soc.*, 1938, **34**, 1093), the contribution of this energy is less than that of the co-ordination energy. The latter is given approximately by $E = \mu_1\mu_2/(r_1 + r_2)^3$ for interaction of two dipoles μ_1 and μ_2 of radii r_1 and r_2, or more closely by $z_1z_2e^2/(r_1 + r_2)^3$ where z_1 and z_2 represent the fractional charges in the interacting atoms of the two dipoles and r_1 and r_2 are the effective radii. Thus, in the case of hydroxylic liquids solvation is due largely to the interaction of oxygen and hydrogen atoms of the hydroxyl group with ion or dipole, and consequently the interaction distance $r_1 + r_2$ is probably equal to $\frac{1}{2}r_{OH} + \frac{1}{2}r_{OCl}$ and not to the average radii of the two interacting molecules. Consequently, the co-ordination energy of water and the alcohols is very similar, with the result that the total heat of solvation is approximately constant.

Similarly, the large entropy decreases (the magnitude of which, as already mentioned, cannot be explained by entropy of Born changing) are due primarily to co-ordination of the inner shell resulting in reduced rotation (libration) of the dipoles. The small entropy changes in the case of water and other associated liquids are attributed to the pseudo-crystalline structure of the liquids, as shown by the low entropies of fusion of water and alcohols. Thus solvation of a large dipole or ion pair by several water molecules which become firmly bound may cause a considerable difference in solvation entropy on change of the solvent from water to an organic liquid (*e.g.*, acetone or dioxan).

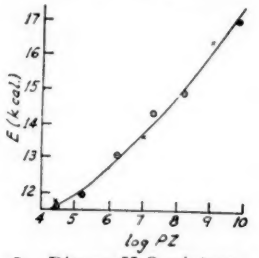
In spite of the formal complexity of the solvation process in binary liquid mixtures, the variation in reaction velocity with changes in solvent composition may be represented simply in terms of this specific solvation. In general, the free energy of solvation of the transition state by one liquid will be much greater than that by less polar liquids, so that a stoicheiometric relation between reaction velocity and concentration of the more polar component is to be expected. Thus in aqueous mixtures, the specific solvation will be due only to water molecules over a wide range of solvent composition. This explains the considerable effect of small quantities of water and alcohol in a solvent of low polarity on

FIG. 2. *Reaction rate vs. mole fraction (benzoyl chloride).*



(*a*) × Acetone–water.
(*b*) ○ Dioxan–water.

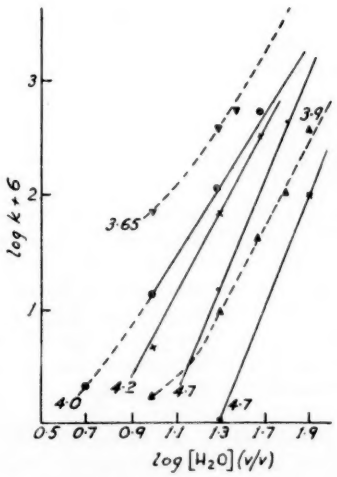
FIG. 3. *E vs. log* PZ.



○ Dioxan–H_2O mixture.
× Acetone–H_2O mixtures.

FIG. 4. *Log k vs. log* [H_2O] *for* S_N1 *reactions in mixed solvents.*

△ Bu^tCl at 25° in EtOH–H_2O mixtures.
● CHPhMeCl at 50° in acetone–water.
× Ph_3·CHCl at 25° in acetone–water.
○ Bu^tBr at 25° in acetone–water.
▽ Bu^tBr at 25° in EtOH–H_2O.
✱ Bu^tCl in 80% acetone–water and 50% dioxan–H_2O.
– – – – Conditions with varying *E*.



conductivity (Hartley and Evans, *Phil. Mag.*, 1935, **15**, 610), rate of reaction (Farinacci and Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 3542; Swain and Eddy, *ibid.*, 1948, **70**, 119), and other kinetic phenomena, although the effect on dielectric constant is small.

In Fig. 2 the velocity constants at 25° measured in dioxan– and acetone–water mixtures are plotted against the mole-fraction of water, and shown to be independent of the second component of the mixture. This may be attributed to the specific solvation of the transition state by water molecules, supported by the observation that an identical *E*–log *PZ* relation is obtained with both mixtures (Fig. 3).

On this basis, ionisation will occur only when the transition state is surrounded by a critical number of water molecules. A random distribution of molecules in the solvent being assumed, the probability P_1 of a water molecule's being adjacent to an RX molecule is given by n_1v_1/V, where n_1 is the number of water molecules of volume v_1 in a volume V

of solvent containing one RX molecule. This volume is composed only of water and inert solvent molecules if the concentration of RX is low so that $V \simeq n_1v_1 + n_2v_2$ and $P_n \simeq n_1v_1/(n_1v_1 + n_2v_1) \equiv$ volume ratio of water in the solvent.

For the simultaneous arrangement of n water molecules around the central RX molecule, the probability $P_n = (v/V)^n$. Thus, for these reactions, $\log P_n = n \log (v_1/V)$.

A relation of this type would be expected to hold approximately except in regions of low and high water content. In the first case solvation by the second component may become important with a consequent rise in E (see Fig. 1), and in the second case the uniform distribution of water molecules is destroyed by clusters which are formed because the association energy of water molecules is greater than that between water and solvent. The available data, given in Fig. 4, show that a linear relation between $\log k$ and $\log v_1/V$ is obeyed over a considerable range of solvent composition for several S_N1 reactions, and from the slope of the graphs values of $4 \pm 0{\cdot}5$ are obtained for n.

The Influence of Hydroxyl Ions.—As hydroxyl ions increase the rate of S_N2 reactions considerably, but have little or no effect on S_N1 reactions, the ratio of the rate constants for alkaline and neutral reactions has been widely used as a semi-quantitative measure of the bimolecular reaction (Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603). Thus values of 10^4—10^5 are obtained for this ratio for S_N2 reactions, whereas in S_N1–S_N2 intermediate cases values of 10^2—10^3 have been recorded. Previous results (Part I) have shown that this ratio (k_{OH}/k_{H_2O}) for unsubstituted benzoyl chloride in 50% aqueous acetone is approximately 600, thus supporting the contention that benzoyl chloride reacts by a mechanism between the S_N2 and the S_N1 mechanism in highly aqueous media.

It was surpising to find that the ratio is of the order of 10^4 for both the *p*-nitro- and the *p*-methoxy-compound in 25% aqueous acetone (Table 5), the value for the former being approximately twice the latter. This difference is in agreement with the greater tendency of the *p*-methoxybenzoyl chloride to react by the S_N1 mechanism but is much smaller than predicted. As the choice of solvent is arbitrary, it is instructive to consider the effect of varying the solvent on the rate ratio. As the effect of water concentration is large in the case of the *p*-methoxy-compound and small in the case of the *p*-nitro-compound, the following order would be expected as the water concentration decreases: (k_{OH}/k_{H_2O})*p*-MeO > (k_{OH}/k_{H_2O})*p*-NO_2.

TABLE 5. *The effect of* OH^- *on the rate of hydrolysis of* p-*nitro- and* p-*methoxybenzoyl chloride.*

$10^3 \times$ Concn. of: chloride	OH^-	k_2, l. mole^{-1} sec.$^{-1}$	Mean	$10^3 \times$ Concn. of: chloride	OH^-	k_2, l. mole^{-1} sec.$^{-1}$	Mean
p-Nitrobenzoyl chloride at 0·2° in 25% H_2O–$COMe_2$ (v/v)				*p*-Methoxybenzoyl chloride at 0·2° in 25% H_2O–$COMe_2$ (v/v)			
1·654	3·528	6·632		2·424	5·790	0·404	
1·587	,,	6·955	6·816	2·612	,,	0·408	0·405
1·496	,,	6·862		2·548	,,	0·403	
1·150	2·612	7·135		1·768	3·925	0·408	
1·091	,,	6·764	6·884	1·652	,,	0·405	0·408
1·262	,,	6·754		1·852	,,	0·410	
1·042	2·201	6·684		1·067	2·238	0·403	0·408
0·982	,,	6·508	6·593	0·981	,,	0·410	
0·957	,,	6·587		0·892	,,	0·411	

This suggests that the S_N2 tendency is greater in the case of the *p*-methoxy-compound if the hydroxide-ion effect is taken as a criterion. This is not so, however, as shown by the following absolute rates and activation energies:

(k_{OH})*p*-MeO < (k_{OH})*p*-NO_2, (k_{H_2O})*p*-MeO ≪ (k_{H_2O})*p*-NO_2, and (E_{H_2O})*p*-MeO ≫ (E_{H_2O})*p*-NO_2.

This anomaly shows that the values of k_{OH}/k_{H_2O} have no simple fundamental significance when compared for reactions in a particular solvent. In the present case it follows that the reaction with hydroxyl ions is less sensitive to substitution than the reaction with water molecules, which appears to be the reverse of Hinshelwood, Laidler, and Timm's generalisation (*J.*, 1938, 848). Their predictions only hold, however, for a series of compounds with similar transition states, whereas the structures of the solvolytic transition

states of the *p*-nitro- and the *p*-methoxy-compound differ considerably (Brown and Hudson, *J.*, 1953, 883).

TABLE 6. *The effect of* OH^- *on the rate of hydrolysis of* 2 : 4 : 6-*trimethyl-benzoyl and -benzyl chloride.*

	$10^3 \times$ Concn. of: chloride	OH^-	10^4k_1, sec.$^{-1}$	Mean	10^4k_1, sec.$^{-1}$ (solvolysis)
2 : 4 : 6-Trimethylbenzoyl chloride at 0·2° in 5% H_2O–$COMe_2$ (v/v)	1·873	1·800	15·36	15·36	15·84
	1·724	,,	15·70		
	1·931	,,	15·01		
2 : 4 : 6-Trimethylbenzyl chloride at 20·4° in 50% H_2O–$COMe_2$	19·73	27·11	105·3	104·1	103·2
	18·12	,,	102·9		
			10^3k_2, l. mole^{-1}/sec.$^{-1}$	Mean	
2 : 4 : 6-Trimethylbenzyl chloride at 30·0° in 25% H_2O–$COMe_2$	16·25	13·12	4·257	4·306	0·134
	15·17	,,	4·356		

The abnormally high value of k_{OH}/k_{H_2O} for the *p*-methoxy-compound in solvents of low water content may be due to repression of the electromeric effect, which is brought into play by the charge separation in the C–Cl bond and tends to reduce the rate of the solvolysis, by the strongly nucleophilic hydroxyl ion. In comparison, a water molecule is weakly nucleophilic, so that the influence is greater and the bond-breaking process becomes more dominant.

Increasing the water content has a considerable effect on the rate ratio for *p*-methoxybenzoyl chloride and almost no effect on that for the *p*-nitrobenzoyl chloride. Thus in media of high water content, $(k_{OH}/k_{H_2O})p\text{-MeO} \ll (k_{OH}/k_{H_2O})p\text{-NO}_2$. This is in agreement with the relative rates of the *p*-methoxy- and the unsubstituted chloride, and the high activation energy of the hydrolysis of *p*-methoxybenzoyl chloride, and supports the contention that a gradual change from an S_N2 to an S_N1 mechanism is produced by increasing the polarity of the solvent.

Finally, it is observed that an accumulation of electron-releasing groups in the benzene nucleus causes the hydrolysis to proceed by the ionisation mechanism even in solvents of low water content. Thus addition of hydroxyl ions has no effect on the rate of hydrolysis of 2 : 4 : 6-trimethylbenzoyl chloride in 95% aqueous acetone (Table 6). This acid chloride reacts much faster than the corresponding benzyl chloride, the rate of which is increased by the addition of hydroxyl ions in 25% aqueous acetone.

This supports the conclusion that, under suitable conditions, acid chlorides may be hydrolysed by the S_N1 mechanism at a much greater rate than the corresponding benzyl chlorides, and that this mechanism is very sensitive to substituent and solvent changes.

QUEEN MARY COLLEGE, LONDON, E.1. [*Received, May 12th,* 1953.]

---

674. *Urea and Related Compounds. Part III.* Alternative Syntheses of Sulphenylureas.*

By FREDERICK KURZER.

The synthesis of *N*-aryl-*N'*-arylsulphenylureas from aromatic *iso*cyanates and sulphenamides confirms their structure previously suggested (Part II *). Alternative methods of preparing members of other new series of sulphenylureas are described.

N-ARYL-*N'*-ARYLSULPHENYLUREAS are obtained by the interaction of arylureas with sulphenyl chlorides in benzene (Geigy, Swiss P. 261,774), or with sulphenyl or sulphinyl chlorides in pyridine (Part II *). The structure originally assigned to *N*-aryl-*N'*-arylsulphenylureas on the basis of their oxidation to sulphonylureas of known formulæ (cf. Part II *) has now been confirmed by an unequivocal synthesis. The reaction between aryl *iso*cyanates and sulphenamides was found to yield *N*-aryl-*N'*-arylsulphenylureas

* Part II, *J.*, 1953, 549.

(equation 1) which proved identical with specimens prepared from the corresponding sulphenyl chloride and arylurea (equation 2).

$$R'S{\cdot}NH_2 + R{\cdot}NCO \longrightarrow R'S{\cdot}NH{\cdot}CO{\cdot}NHR \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$R'SCl + R{\cdot}NH{\cdot}CO{\cdot}NH_2 \longrightarrow R'S{\cdot}NH{\cdot}CO{\cdot}NHR + HCl \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In agreement with Lecher and his co-workers' observations (*Ber.*, 1925, **58**, 409), it was not found possible to prepare toluene-*p*-sulphenamide from the corresponding sulphenyl chloride. The action of aqueous or liquid ammonia on toluene-*p*-sulphenyl chloride gave, in each case, moderate yields of ditoluene-*p*-sulphenimide. The fairly readily accessible *o*-nitrobenzenesulphenamide (Zincke and Farr, *Annalen*, 1912, **391**, 75) was therefore chosen for further experiments. In boiling triethylamine suspension, this sulphenamide reacted with phenyl or *p*-diphenylyl *iso*cyanate and gave satisfactory yields of the required sulphenylureas. Careful exclusion of moisture and the presence of the tertiary base were critical for the success of these condensations. The importance of basic catalysts in addition reactions involving aryl *iso*cyanates has been demonstrated by Baker and Gaunt (*J.*, 1949, 9). The production of substituted ureas from *iso*cyanates and amines, however, proceeds rapidly without the addition of tertiary bases; here, the basic nature of the amines is probably responsible for self-catalysing effects. Although sulphenamides possess very weakly basic properties, these are not sufficiently pronounced to permit salt formation in aqueous solution (Kharasch *et al.*, *Chem. Reviews*, 1946, **39**, 269, 318). The slightly basic nature of sulphenamides is probably further reduced, in the present case, by the presence of the nitro-group which is known, for example, to exert a strong weakening in the basicity of *o*-nitroaniline ($K_b = 1{\cdot}0 \times 10^{-14}$) in comparison with that of aniline ($K_b = 1{\cdot}4 \times 10^{-10}$). The absence, in sulphenamides, of basic properties which might be responsible for autocatalytic effects would explain the pronounced influence of tertiary bases on the rate of the *iso*cyanate–sulphenamide condensation.

Attempts to extend the present synthesis to the preparation of sulphinylureas were unsuccessful. Owing, no doubt, to the ease of oxidation–reduction reactions involving the sulphinyl group, toluene-*p*-sulphinamide and phenyl *iso*cyanate, under various conditions (cf. Experimental), which had proved effective in the sulphonyl- or sulphenyl-series, failed to yield the expected sulphinylureas; in their place, minute yields of the corresponding *N*-aryl-*N'*-arylsulphonylureas were sometimes obtained.

Reactions that might afford representatives of simpler sulphenylurea series were also examined. Urea and *o*-nitrobenzenesulphenyl chloride in pyridine produced either mono- or di-sulphenylurea, depending on which of the reactants was present in excess (equations 3 and 4). Equimolecular proportions of the reactants gave, in addition to small quantities of the disulphenylurea, *N*-*o*-nitrobenzenesulphenylurea as main product (50—55%); *NN'*-di-*o*-nitrobenzenesulphenylurea was obtained as the sole product in good yields when a large excess of the sulphenyl halide was employed. Varying quantities of the acid halide, even when not present in excess, were consumed in a side reaction resulting in the formation of diaryl disulphide. The structures assigned to the mono- and di-sulphenylureas are not established unequivocally by the above mode of formation, but are supported by the following considerations. In contrast to sulphonyl halides which, in the first instance, attack the urea or thiourea molecule at the oxygen (or sulphur) atom (*Chem. Reviews*, 1952, **50**, 1, 16), sulphinyl and sulphenyl chlorides have been proved to substitute at the free amide-nitrogen in arylureas (Part II, *loc. cit.*); analogous *N*-substitution in urea itself may therefore be reasonably expected. Moreover, *O*-sulphenyl*iso*ureas $R'SO{\cdot}C(:NH)NH_2$, in common with *O*-sulphonyl*iso*ureas (Short *et al.*, *Chem. and Ind.*, 1949, 419; Dixon *et al.*, *J.*, 1907, **91**, 130; 1920, **117**, 720), are likely to be unstable, particularly in pyridine solution. The suggested structure for *N*-*o*-nitrobenzenesulphenylurea was finally confirmed by two additional syntheses: fusion of *o*-nitrobenzenesulphenamide with urea at 150—160° gave moderate yields of the compound, with evolution of ammonia (equation 5); and it was also prepared from *N*-*o*-nitrobenzenesulphenyl-*O*-methyl*iso*urea of known structure (see below).

$$3R'SCl + 2NH_2{\cdot}CO{\cdot}NH_2 \begin{cases} \longrightarrow R'S{\cdot}NH{\cdot}CO{\cdot}NH_2 + HCl \quad . \quad . \quad . \quad . \quad . \quad (3) \\ \longrightarrow R'S{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}SR' + 2HCl \quad . \quad . \quad . \quad . \quad (4) \end{cases}$$

$$R'S{\cdot}NH_2 + NH_2{\cdot}CO{\cdot}NH_2 \longrightarrow R'S{\cdot}NH{\cdot}CO{\cdot}NH_2 + NH \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The behaviour of *iso*ureas in this reaction was also examined. Methyl*iso*urea reacted with *o*-nitrobenzenesulphenyl chloride in acetone–aqueous alkali, to form the expected *O*-methyl-*N*-*o*-nitrobenzenesulphenyl*iso*urea (equation 6). Small yields of a second product, regarded as *NN'*-di-*o*-nitrobenzenesulphenyl-*O*-methyl*iso*urea (equation 7) were also isolated. When ethyl*iso*urea was employed in this reaction, the disulphenated *iso*urea (R = Et) became the main product. The proposed structure of the last two compounds is based on a knowledge of their composition, molecular weights, and mode of formation. Since the oxygen is blocked by alkyl groups in the *iso*urea structure, attachment of the sulphenyl groups must necessarily occur on the nitrogen. In view of the greater difficulty of introducing an acyl radical into an acylamino- than into an unsubstituted amino(or imino)-residue, the symmetrically *NN'*-disubstituted *iso*urea structure is the preferred formula for the disulphenyl*iso*ureas obtained in the present reaction.

$$R'SCl + NH_2\cdot C(OR){:}NH + NaOH \longrightarrow R'S\cdot NH\cdot C(OR){:}NH + NaCl + H_2O \quad . \quad . \quad (6)$$

$$2R'SCl + NH_2\cdot C(OR){:}NH + 2NaOH \longrightarrow R'S\cdot NH\cdot C(OR){:}NSR' + 2NaCl + 2H_2O \quad . \quad (7)$$

In pyridine the interaction of methyl*iso*urea and sulphenyl halide proceeded with simultaneous loss of the methyl group, resulting in the direct formation of *N*-*o*-nitrobenzenesulphenyl- and *NN'*-di-*o*-nitrobenzenesulphenyl-urea. In this reaction, the intermediate *O*-methyl-*N*-sulphenyl*iso*urea appears to be immediately dealkylated by halide ions provided by the sulphenyl chloride, the resulting alkyl halide probably being removed as the alkylpyridinium salt (equation 8). Support for this view was provided by experiments which showed that *O*-methyl-*N*-*o*-nitrobenzenesulphenyl*iso*urea, though stable when heated by itself in pyridine, was converted into the above mono- and disulphenylureas when its pyridine solution was treated with an excess of sulphenyl chloride (equation 9). The fact that the halogen (presumably in the form of chloride ions) was concerned in initiating the elimination of the alkyl group appeared to be confirmed by the observation that pyridinium chloride was equally effective in dealkylating the substituted methyl*iso*urea (equation 10), and afforded, incidentally, an excellent method of converting *O*-methyl-*N*-*o*-nitrobenzenesulphenyl*iso*urea (of known structure) into *N*-*o*-nitrobenzenesulphenylurea, thus confirming the constitution of the latter. *O*-Alkyl*iso*ureas and their *N*-sulphonyl derivatives are readily dealkylated by short boiling with ethanolic hydrochloric acid, which eliminates the *O*-substituent as the alkyl chloride (McKee, *Amer. Chem. J.*, 1901, **26**, 230; Cox *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 300; 1942, **64**, 2225; Haak, U.S.P. 2,312,404). In the corresponding sulphenyl series, even the briefest treatment with alcoholic hydrochloric acid caused further hydrolytic decomposition, and only small yields of the desired *N*-sulphenylurea could be isolated. Pyridinium chloride in pyridine is therefore a useful alternative dealkylating agent which combines equal effectiveness with far milder action.

$$3R'SCl + 2NH_2\cdot C(OR){:}NH + 3C_5H_5N \longrightarrow R'S\cdot NH\cdot CO\cdot NH_2 + R'S\cdot NH\cdot CO\cdot NH\cdot SR' + 2[C_5H_5NR]^+Cl^- + [C_5H_5NH]^+Cl^- \quad (8)$$

$$R'SCl + R'S\cdot NH\cdot C(OR){:}NH + C_5H_5N \longrightarrow R'S\cdot NH\cdot CO\cdot NH\cdot SR' + [C_5H_5NR]^+Cl^- \quad . \quad . \quad . \quad . \quad (9)$$

$$R'S\cdot NH\cdot C(OR){:}NH + [C_5H_5NH]^+Cl^- \longrightarrow R'S\cdot NH\cdot CO\cdot NH_2 + [C_5H_5NR]^+Cl^- \quad . \quad . \quad . \quad . \quad (10)$$

As in all other reactions employing sulphenyl halides in a basic environment, a proportion of the reagent was lost as the disulphide. Under the conditions of the above syntheses, the occurrence of this side-reaction appears to be unavoidable, since *o*-nitrobenzenesulphenyl chloride and certain analogues are known to yield the disulphides when merely heated by themselves in pyridine solution (Moore and Johnson, *J. Amer. Chem. Soc.*, 1935, **57**, 1517). *o*-Nitrobenzenesulphenyl chloride, however, seemed to be more stable in this respect than toluene-*p*-sulphenyl chloride and afforded, in general, better yields of the substituted ureas.

Experimental

M. p.s are uncorrected. The anhydrous triethylamine used in the present experiments was dried by two successive distillations, from potassium hydroxide and phenyl *iso*cyanate, severally. The pyridine used was the commercially available anhydrous grade. The identity of di-*o*-nitrophenyl disulphide was confirmed, whenever applicable, by mixed m. p. determination with authentic material.

N-o-*Nitrobenzenesulphenyl*-N′-*phenylurea*.—(a) *From phenyl* iso*cyanate*. A stirred suspension of *o*-nitrobenzenesulphenamide (1·70 g., 0·01 mole) in anhydrous triethylamine (15 ml.) was treated, during 20 min. at 85°, with a solution of phenyl *iso*cyanate (2·38 g., 0·02 mole) in anhydrous triethylamine (10 ml.). The deep orange suspension was stirred for a further 30 min., then cooled, the supernatant liquid decanted, the residual mass twice stirred with water (2 × 50 ml.), and the semisolid residue boiled with ethanol (60 ml.). The resulting pale yellow granular powder (1·85 g.) was filtered off (filtrate A) and twice crystallised from boiling ethanol (approx. 250 ml. per g. of crude material), giving a small quantity of delicate pale yellow needles of N-o-*nitrobenzenesulphenyl*-N′-*phenylurea*, m. p. 232—234° (decomp.) (Found: C, 54·3; H, 3·7. $C_{13}H_{11}O_3N_3S$ requires C, 54·0; H, 3·8%). The greater part of the product was recovered by fractional evaporation of the mother-liquors (total yield, 1·2—1·4 g., 41—48%), the final fractions of which contained *s*-diphenylurea. Further small quantities of the sulphenylurea were recovered from filtrate A.

(b) *From phenylurea in pyridine*. A solution of phenylurea (1·7 g., 0·0125 mole) in pyridine (25 ml.) was treated, at 25°, in two equal portions, with *o*-nitrobenzenesulphenyl chloride (4·75 g., 0·025 mole; Hubacher, *Org. Synth.*, 1943, Coll. Vol. 2, p. 455). The resulting hot (60°) deep orange liquid was set aside for 15 min. and then stirred into ice-water (150 ml.)–hydrochloric acid (25 ml.). The separated yellow granular solid was boiled with acetone (100 ml.); the undissolved residue (1·25 g.) was collected (filtrate B) and was twice crystallised from ethanol, giving needles of *N*-*o*-nitrobenzenesulphenyl-*N*′-phenylurea, m. p. 234—236° (decomp.), undepressed in admixture with material prepared by method (a) (Found: N, 14·8; S, 11·2. $C_{13}H_{11}O_3N_3S$ requires N, 14·5; S, 11·1%). Filtrate B gave, on fractional evaporation and recrystallisation of the individual crops, further small quantities of the sulphenylurea (total yield, 0·92 g., 25%) and yellow prisms of di-*o*-nitrophenyl disulphide, m. p. 194—195° (1·75 g.).

(c) *From phenylurea in benzene*. A stirred boiling solution of phenylurea (1·36 g., 0·01 mole) in anhydrous benzene (80 ml.) was treated, during 1·5 hr., with *o*-nitrobenzenesulphenyl chloride (2·0 g., 0·011 mole) in benzene (40 ml.). After a further 1·5 hr.' refluxing, during which a yellow crystalline material had begun to appear, the liquid was evaporated in a vacuum to half bulk, and the solid filtered off (filtrate C). Crystallisation from ethanol gave yellow needles of *N*-*o*-nitrobenzenesulphenyl-*N*′-phenylurea, m. p. 234—236° (decomp.), undepressed in admixture with material prepared by methods (a) and (b) (Found: C, 53·9; H, 3·9%). Fractional crystallisation of the material obtained from filtrate C gave, in addition to a further crop of the sulphenylurea (total yield, 0·62 g., 22%), small quantities of di-*o*-nitrophenyl disulphide, m. p. 195°, and much unchanged phenylurea (0·6 g., 44%).

N-p-*Diphenylyl*-N′-o-*nitrobenzenesulphenylurea*.—(a) *From* p-*diphenylyl* iso*cyanate*. *o*-Nitrobenzenesulphenamide (1·70 g., 0·01 mole), suspended in triethylamine (30 ml.), was treated at 85°, during 45 min., with a suspension of *p*-diphenylyl *iso*cyanate (2·45 g., 0·0125 mole) in triethylamine (15 ml.), and stirring at 85° was continued for 1 hr. The separated yellow solid (3·6 g.) was twice crystallised from acetone (approx. 120 ml. per g.) and gave yellow needles of N-p-*diphenylyl*-N′-o-*nitrobenzenesulphenylurea*, m. p. 247—248° (decomp.) (Found: C, 62·9; H, 4·2. $C_{19}H_{15}O_3N_3S$ requires C, 62·5; H, 4·1%). The yield, including material from mother-liquors, was 3·2 g. (87%).

(b) *From* p-*diphenylylurea*. Interaction of *p*-diphenylylurea (2·12 g., 0·01 mole) and *o*-nitrobenzenesulphenyl chloride (3·8 g., 0·02 mole; added in two equal portions at 5 min.' interval) in pyridine (40 ml.) at 50—40° for 20 min., and addition of the orange liquid to dilute hydrochloric acid gave an orange powder (5·45 g.). Fractionation from boiling acetone (500 ml.) gave the less soluble sulphenylurea, m. p. 246—248° (decomp.), undepressed in admixture with material prepared by method (a) (Found: N, 11·8; S, 9·0. $C_{19}H_{15}O_3N_3S$ requires N, 11·5; S, 8·8%) (total yield, 2·75 g., 75%). The fraction most soluble in acetone consisted of yellow prisms of di-*o*-nitrophenyl disulphide, m. p. 195—196° (1·2—1·5 g.).

Attempted Synthesis of an N-Aryl-N′-arylsulphinylurea by Method (a).—Toluene-*p*-sulphinamide (1·55 g., 0·01 mole) (von Braun and Kaiser, *Ber.*, 1923, **56**, 549; Raiford and Hazlett, *J. Amer. Chem. Soc.*, 1935, **57**, 2172) and phenyl *iso*cyanate (1·8—2·4 g., 0·015—0·02 mole) were allowed to react under the following conditions: (i) in boiling benzene (50 ml.) containing triethylamine (2·0 g., 0·02 mole) during 2 hr.; (ii) in pyridine (10 ml.)–triethylamine (5 ml.) at 50° during 30 min., or at 100° during 2 hr.; (iii) in triethylamine (5 ml., refluxing during 1 hr.; or 60 ml. at 85° during 1 hr.). The resulting mixture was extracted with aqueous alkali, and the filtered extracts were acidified with concentrated hydrochloric acid at 0°. A small white precipitate (0·2—0·4 g.) obtained in methods (i) and (iii) was crystallised from benzene–light petroleum and consisted of *N*-phenyl-*N*′-toluene-*p*-sulphonylurea, m. p. and mixed m. p.

(*J.*, 1951, 1258) 171—173° (Found: C, 58·1; H, 5·1. Calc. for $C_{14}H_{14}O_3N_2S$: C, 57·9; H, 4·8%). Considerable quantities of *s*-diphenylurea were recovered in all cases.

Interaction of Urea and o-*Nitrobenzenesulphenyl Chloride.*—A suspension of urea (1·80 g., 0·03 mole) in pyridine (50 ml.), kept at 70°, was treated with *o*-nitrobenzenesulphenyl chloride (6·25 g., 0·033 mole) in 6—8 equal portions during 30 min., the undissolved urea being continuously stirred and crushed. The resulting clear yellow solution was kept at 70° for a further 10 min., then stirred into ice (100 g.)–water (100 ml.)–concentrated hydrochloric acid (50 ml.), and the yellow powder collected and washed with water. The dried material (5·8 g.) was extracted with boiling acetone (4 × 250 ml.), and the insoluble residue filtered from the hot solution (extracts A). The residual yellow powder (1·2 g.), crystallised from boiling nitrobenzene (80 ml.), gave pale yellow needles (0·85 g., 8%) of NN'-*di*-o-*nitrobenzenensulphenylurea*, m. p. 299—300° (decomp. with explosive violence) (Found: C, 42·85; H, 2·8; N, 15·1; S, 17·6. $C_{13}H_{10}O_5N_4S_2$ requires C, 42·6; H, 2·7; N, 15·3; S, 17·5%), practically insoluble in the usual organic solvents.

The acetone extracts A were evaporated in two stages (to approx. 500 and 200 ml.), and the separated material collected. It consisted in each case of yellow needles (m. p. 225—230°, followed by decomp. at 270°; 3·2—3·5 g., 50—55%) which gave, after two crystallisations from acetone (200 ml. per g.) or (preferably) ethanol (120 ml. per g.), needles of N-o-*nitrobenzenesulphenylurea*, m. p. 235—238° (decomp. to an orange-brown melt, followed by characteristically vigorous decomp. at 272—275°; to obtain reproducible values for this decomp. point, the sample must be pressed down in the m. p. tube to form a compact mass approx. 2 mm. in depth) (Found: C, 39·7; H, 3·6; N, 19·6; S, 15·3. $C_7H_7O_3N_3S$ requires C, 39·4; H, 3·3; N, 19·7; S, 15·0%). The final acetone filtrates were allowed to evaporate spontaneously at room temperature; they deposited further small quantities (0·5—0·8 g., 8—13%) of powdery sulphenylurea, and large yellow prisms. The latter (0·5—0·8 g.), when mechanically separated and crystallised from acetone, gave di-*o*-nitrophenyl disulphide, m. p. 194—195°.

Interaction of urea (0·01 mole) with an excess of *o*-nitrobenzenesulphenyl chloride (0·033 mole) (conditions, and isolation of the products, as above) gave almost entirely *NN'*-di-*o*-nitrobenzenesulphenylurea (72—75%), the excess of the sulphenyl chloride being isolated as di-*o*-nitrophenyl disulphide. Only small yields of *N*-*o*-nitrobenzenesulphenylurea (1—2%) were obtained in some but not all experiments, by careful fractionation of the acetone extracts.

Interaction of Urea and o-*Nitrobenzenesulphenamide.*—A flask containing an intimate mixture of finely powdered urea (1·20 g., 0·02 mole) and *o*-nitrobenzenesulphenamide (1·70 g., 0·01 mole) was placed in a paraffin bath kept at 150°. The mixture melted completely within 5 min. on stirring. The bath-temperature was then slowly raised so that the melt, which evolved ammonia, reached a temperature of 160—165° within 10 min. and was stirred at this temperature for an additional 15 min. Towards the end, the interface between the two phases gradually disappeared and partial solidification occurred, a deep brown paste-like substance being obtained. The cooled solidified mass was broken up by being stirred with water (2 × 10 ml.), and the yellow powder was collected (1·75 g.) and dissolved in boiling acetone (4 × 30 ml.). Fractional spontaneous evaporation of the combined acetone extracts gave a series of crystalline crops, the first three of which were combined [total, 0·6—0·8 g., 29—38%; m. p. 235—270° (decomp.)] and gave, on crystallisation from acetone or ethanol, yellow needles of *N*-*o*-nitrobenzenesulphenylurea, m. p. 235—240° (decomp. to orange-brown droplets, followed by vigorous decomp. at 272°). The final crops consisted of di-*o*-nitrophenyl disulphide (0·6 g.).

Interaction of O-*Methylisourea and* o-*Nitrobenzenesulphenyl Chloride in Alkali.*—A solution of methyl*iso*urea hydrochloride (2·20 g., 0·02 mole) in aqueous sodium hydroxide (12% w/v; 6·6 ml., 0·02 mole), diluted with acetone (20 ml.), was treated with shaking, during 12—15 min. at 0—5°, with *o*-nitrobenzenesulphenyl chloride (3·80 g., 0·02 mole) in acetone (25 ml.). Towards the end of the addition, the alkalinity (towards litmus) of the mixture was maintained by simultaneous addition of an equivalent of sodium hydroxide (12%; 6·6 ml.). The granular orange precipitate (1·4—1·6 g.) separating from the resulting deep red liquid was collected (solid A). The filtrate separated into two layers; the aqueous phase (5—10 ml.) containing sodium chloride was discarded. The deep red aqueous acetone solution was set aside for several hours, then slowly diluted with water (12—15 ml.), and the final fraction of separated di-*o*-nitrophenyl disulphide (0·25 g., 8%) filtered off. Careful dilution of the filtrate with water (to 120—150 ml.) precipitated deep scarlet crystals (0·9—1·35 g., 20—30%). Crystallisation from benzene–light petroleum (5, and 5 ml. per g.; recovery 50—60% per crystallisation) gave lustrous dark-scarlet prism or plates of O-*methyl*-N-o-*nitrobenzenesulphenyl*iso*urea*, m. p. 114—115° [Found: C, 42·3; H, 4·2; N, 18·8; S, 13·9%; *M* (Rast), 217; *M* (cryoscopically, in

naphthalene), 240. $C_8H_9O_3N_3S$ requires C, 42·3; H, 4·0; N, 18·5; S, 14·1%; *M*, 227], highly soluble in acetone, ethanol, or warm benzene.

Solid A (collected from three experiments, 4·5 g.) was extracted with boiling acetone (4 × 25 ml.), and the residual orange powder [m. p. 203—205° (decomp.); 1·50 g., 6·5% calc. on the methyl*iso*urea] was collected (acetone filtrates B). Dissolution of the finely powdered solid in boiling acetone (250 ml. per g.), rapid filtration of the hot liquid, followed by evaporation under reduced pressure to half volume, and a further crystallisation from acetone gave massive deep-orange prisms of O-*methyl*-NN′-*di*-o-*nitrobenzenesulphenyliso*urea, m. p. 203—205° (decomp.) [Found: C, 44·5; H, 3·2; N, 14·4; S, 16·6%; *M* (cryoscopically, in naphthalene), 405. $C_{14}H_{12}O_5N_4S_2$ requires C, 44·2; H, 3·2; N, 14·7; S, 16·8%; *M*, 380]. The acetone filtrates B deposited, on evaporation to small volume, a granular yellow solid (2·5 g.), which consisted largely of di-*o*-nitrophenyl disulphide.

The use of a large excess of methyl*iso*urea hydrochloride, or substitution of potassium carbonate for sodium hydroxide as acid-absorbing agent, did not substantially improve the yields of *O*-methyl-*N*-*o*-nitrobenzenesulphenyl*iso*urea.

Interaction of O-*Ethyliso*urea *and* o-*Nitrobenzenesulphenyl Chloride in Alkali.*—Ethyl*iso*urea hydrochloride (1·25 g., 0·01 mole) was treated with *o*-nitrobenzenesulphenyl chloride (3·80 g., 0·02 mole) in acetone–aqueous alkali (conditions as for methyl*iso*urea). The acetone layer of the resulting clear two-phase system was allowed to evaporate spontaneously, the residual solid was warmed with acetone (10 ml.), and the undissolved yellow powder filtered off (solid A). Dilution of the deep orange filtrate with ethanol (10 ml.), and partial spontaneous evaporation, yielded massive prisms which gave, on further crystallisation from acetone–ethanol, deep orange prisms of O-*ethyl*-NN′-*di*-o-*nitrobenzenesulphenyliso*urea*, m. p. 143—144° (decomp.) (Total yield, including material from mother-liquors, 1·75—2·15 g., 45—55%) [Found: C, 45·8, 45·7; H, 3·7, 3·8; N, 13·9, 14·0; S, 16·1, 16·3%; *M* (Rast), 345; *M* (cryoscopically, in naphthalene), 370. $C_{15}H_{14}O_5N_4S_2$ requires C, 45·7; H, 3·55; N, 14·2; S, 16·2%; *M*, 394]. Solid A (0·25—0·50 g.) was crystallised from ethanol and consisted mainly of di-*o*-nitrophenyl disulphide.

Interaction of O-*Methyliso*urea *and* o-*Nitrobenzenesulphenyl Chloride in Pyridine.*—A stirred suspension of methyl*iso*urea hydrochloride (2·20 g., 0·02 mole) in pyridine (20 ml.) was treated at 45—50° with *o*-nitrobenzenesulphenyl chloride (5·70 g., 0·03 mole) in portions during 15 min., and the resulting deep-red, clear liquid kept at 50—60° for a further 15 min. The orange-yellow powder which separated when the liquid was poured into ice-water (150 ml.)–concentrated hydrochloric acid (20 ml.) was collected (5·50 g.) and boiled with acetone (4 × 50 ml.). The pale yellow residual powder (1·20 g., 16%) was *NN*′-di-*o*-nitrobenzenesulphenylurea, m. p. 300° (decomp.) (from nitrobenzene), undepressed by material prepared from urea (see above) (Found: N, 15·2. Calc. for $C_{13}H_{10}O_5N_4S_2$: N, 15·3%). The combined acetone extracts deposited, on spontaneous evaporation, a granular yellow solid (total, 1·58 g., 37%) which gave, on crystallisation from ethanol, silky needles of *N*-*o*-nitrobenzenesulphenylurea, m. p. 235—240° (decomp. to orange-brown droplets, followed by decomp. at 270—272°) (Found: C, 39·9; H, 3·4; N, 19·4. Calc. for $C_7H_7O_3N_3S$: C, 39·4; H, 3·3; N, 19·7%). Yellow prisms of di-*o*-nitrophenyl disulphide (0·8—1·0 g.; m. p. 195—196°) gradually separated from the final acetone filtrates.

NN′-*Ditoluene*-p-*sulphenylurea.*—The crude product of the interaction of methyl*iso*urea hydrochloride (1·10 g., 0·01 mole) and toluene-*p*-sulphenyl chloride (4·75 g., 0·03 mole) in pyridine (details as above) consisted of an orange oil which was heated with ethanol (6 ml.). The solid which separated on cooling was filtered off (filtrate A). Crystallisation from ethanol (200 ml. per g.) gave colourless needles of NN′-*ditoluene*-p-*sulphenylurea*, m. p. 204—206° (decomp.) (0·5—0·6 g., 17—20%) (Found: C, 58·95; H, 5·2; N, 8·85; S, 20·6. $C_{15}H_{16}ON_2S_2$ requires C, 59·2; H, 5·3; N, 9·2; S, 21·05%). Filtrates A contained di-*p*-tolyl disulphide, m. p. and mixed m. p. 45—46°.

N-*Sulphenylureas from* O-*Methyl*-N-o-*nitrobenzenesulphenyliso*urea.—(*a*) *O*-Methyl-*N*-*o*-nitrobenzenesulphenyl*iso*urea (0·46 g., 0·002 mole) and pyridinium chloride (0·46 g., 0·004 mole) were added to pyridine (10 ml.), and the suspension was kept at 50—60° for 30 min. The resulting solution, which had changed from deep red to pale orange, was added to hydrochloric acid (2N; 50 ml.) at 0° and the precipitated yellow powder (0·42 g.) collected. Crystallisation from boiling acetone (40 ml.) gave needles (0·32 g., 75%) of *N*-*o*-nitrobenzenesulphenylurea, m. p. and mixed m. p. (with material prepared as described above) 235—240° (decomp. to orange brown droplets, followed by vigorous decomp. at 270—272°).

(*b*) The use of *o*-nitrobenzenesulphenyl chloride (0·57 g., 0·003 mole) in place of pyridinium chloride gave a crude product (0·75 g.) which was boiled with acetone (30 and 10 ml.). The acetone-insoluble part (0·22 g., 30%) consisted of *NN*′-di-*o*-nitrobenzenesulphenylurea,

m. p. 300° (decomp. explosively) (from nitrobenzene). Fractional crystallisation of the acetone-soluble material gave *N*-*o*-nitrobenzenesulphenylurea (0·15 g., 35%) and di-*o*-nitrophenyl disulphide.

(*c*) *O*-Methyl-*N*-*o*-nitrobenzenesulphenyl*iso*urea was recovered unchanged when heated by itself in pyridine solution at 50—60° for ½ hr.

Ditoluene-p-*sulphenimide*.—To aqueous ammonia (*d* 0·88; 80 ml.), covered by a layer of ether (50 ml.), a solution of toluene-*p*-sulphenyl chloride (Lecher *et al.*, *Ber.*, 1925, **58**, 409) (7·9 g., 0·05 mole) in anhydrous ether (80 ml.) was added dropwise during 20 min. with good stirring, the addition of each drop causing a transient deep violet colour. The resulting reddish-orange ethereal layer was washed with dilute hydrochloric acid (insufficient to render the ethereal solution acid) and water until neutral. The semisolid residue obtained after the removal of the solvent in a vacuum below 30° was stirred with cold methanol (2 × 10 ml.) and cooled to 0°. The crystalline residue (2·4 g.; methanolic filtrate A) was twice crystallised from boiling methanol, giving needles of *ditoluene*-p-*sulphenimide*, m. p. 109—111° (total yield, 1·65 g., 25%) (Found: C, 64·2; H, 5·5. $C_{14}H_{15}NS_2$ requires C, 64·4; H, 5·75%). The methanolic filtrate A contained di-*p*-tolyl disulphide, m. p. 44—45° (3·2 g., 52%). Essentially the same results were obtained by addition of a concentrated ethereal solution (50% w/v) of toluene-*p*-sulphenyl chloride to liquid ammonia.

The writer gratefully acknowledges a grant from the Research Fund of the Chemical Society.

Royal Free Hospital School of Medicine,
(University of London), W.C.1.

[*Received, May 29th,* 1953.]

---

675. *The Isomerisation of* iso*Flavones.*

By W. B. Whalley.

Conditions are detailed for the demethylation of 5 : 7 : 2′-trimethoxy*iso*flavone (I; R = Me) (Whalley, *J. Amer. Chem. Soc.*, 1953, **75**, 1059) to 5 : 7 : 2′-trihydroxy*iso*flavone (I; R = H). The removal, by the same methods, of the methoxyl groups from 5 : 7 : 2′- or 5 : 7 : 4′-trimethoxy-8-methyl*iso*flavone gave a mixture of the corresponding trihydroxy-8- and -6-methyl*iso*flavones (Whalley, *Chem. and Ind.*, 1953, 277).

Difficulties in demethylation of 5 : 7 : 2′-trimethoxy- (I; R = Me) and 5 : 7 : 2′-trimethoxy-8-methyl-*iso*flavone (II; R = Me) have been previously described (Whalley, *J. Amer. Chem. Soc.*, 1953, **75**, 1059). An improved technique is now reported, and cyclisation of several deoxybenzoins to the corresponding 2-hydroxy*iso*flavanones (Whalley, *loc. cit.*) is described.

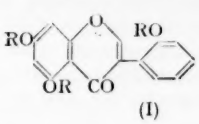
Attempts to demethylate 5 : 7 : 2′-trimethoxy*iso*flavone (I; R = Me) by hydriodic acid which had been purified by *distillation* over red phosphorus in the usual manner gave a resin from which only a trace of 5 : 7 : 2′-trihydroxy*iso*flavone (I; R = H) was obtained. Use of hydriodic acid which had been refluxed with red phosphorus until colourless and then filtered, or, better, which had "phosphorous acids" added (*e.g.*, as a stabiliser, as in the product marketed by Merck & Co., Rahway, N.J.) gave a superior result. Even so the yield was poor, and better results were obtained by using aluminium chloride, though its quality is important. When this work was almost complete the synthesis, by a different method, of 5 : 7 : 2′-trihydroxy*iso*flavone was described by Baker, Harborne, and Ollis (*Chem. and Ind.*, 1952, 1058)

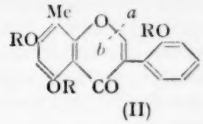
Demethylation of 5 : 7 : 2′-trimethoxy-8-methyl*iso*flavone (II; R = Me) with stabilised hydriodic acid or aluminium chloride furnished (in moderate yield) 5 : 7 : 2′-trihydroxy-8-methyl- (II; R = H) and 5 : 7 : 2′-trihydroxy-6-methyl-*iso*flavone (III; R = R′ = H) (Whalley, *Chem. and Ind.*, 1953, 277), best separated after methylation. 5 : 7 : 2′-Trimethoxy-6-methyl*iso*flavone (III; R = R′ = Me) was synthesised by the conversion of 5 : 7 : 2′-trihydroxy*iso*flavone (I; R = H) into 5-hydroxy-7 : 2′-dimethoxy-6-methyl*iso*flavone (III; R = Me, R′ = H) by means of methyl iodide in methanol containing sodium

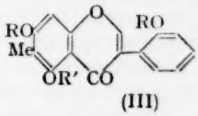
methoxide (Baker and Robinson, *J.*, 1926, 2713; Whalley, *loc. cit.*), followed by full methylation with methyl sulphate and potassium carbonate.

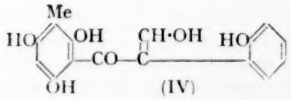
The possibility that the methyl ether of the second demethylation product of (II; R = Me) was (V; R = Me), formed by way of the intermediate (IV) (cf. Whalley, *loc. cit.*) and yet equatable with the methylation product of 5 : 7 : 2′-trihydroxy*iso*flavone (I; R = H) because of a similar rearrangement occurring during the methylation of (I; R = H), was excluded as follows. Alkaline degradation of (III; R = R′ = Me) gave 2-hydroxy-4 : 6 : 2′-trimethoxy-5-methyldeoxybenzoin (VII), converted by ethylation into 2-ethoxy-4 : 6 : 2′-trimethoxy-5-methyldeoxybenzoin (VI; R = Me), which was identical with a specimen prepared by the methylation of 2-ethoxy-4 : 6-dihydroxy-2′-methoxy-5-methyldeoxybenzoin (VI; R = H), obtained by the Hoesch condensation of 4-ethoxy-2 : 6-dihydroxytoluene and 2-methoxybenzyl cyanide.

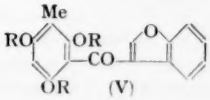
Alkaline degradation of the unknown 3-aroylcoumarone type (V) might be expected to proceed similarly to that of the isomeric *iso*flavone (III; R = R′ = Me) to give, however,

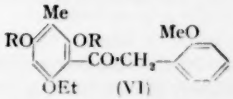

(I)


(II)


(III)


(IV)

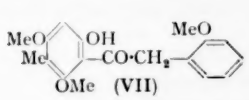

(V)

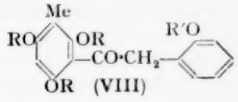

(VI)

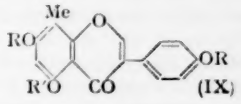
instead of the ketone (VII), 2′-hydroxy-2 : 4 : 6-trimethoxy-3-methyldeoxybenzoin (VIII; R = Me, R′ = H) which would be converted by ethylation into 2′-ethoxy-2 : 4 : 6-trimethoxy-3-methyldeoxybenzoin (VIII; R = Me, R′ = Et). Condensation of 2-ethoxybenzyl cyanide with *C*-methylphloroglucinol furnished the ketone (VIII; R = H, R′ = Et) which was converted by methylation into the deoxybenzoin (VIII; R = Me, R′ = Et) isomeric, but not identical, with (VI; R = Me).

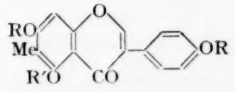
Similarly, demethylation of 5 : 7 : 4′-trimethoxy-8-methyl*iso*flavone (IX; R = R′ = Me) (Whalley, *loc. cit.*) with hydriodic acid during a prolonged period gave 5 : 7 : 4′-trihydroxy-8-methyl*iso*flavone together with small quantities of 5 : 7 : 4′-trihydroxy-6-methyl*iso*flavone (X; R = R′ = H), which was converted by methylation into 5 : 7 : 4′-trimethoxy-6-methyl*iso*flavone (X; R = R′ = Me), identical with a specimen prepared by the methylation of 5-hydroxy-7 : 4′-dimethoxy-6-methyl*iso*flavone (X; R′ = H, R = Me) (Baker and Robinson, *loc. cit.*; Whalley, *loc. cit.*). Partial methylation of 5 : 7 : 4′-trihydroxy-8-methyl*iso*flavone (IX; R = R′ = H) gave its 7 : 4′-dimethyl ether.

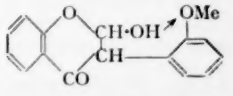
The postulate (Whalley, *loc. cit.*) that the *iso*flavone system may open across *a*—*b* in (II) during demethylation is thus confirmed, at least for certain cases, and this supports the suggestion that the difficulties in demethylation of 2′-methoxy*iso*flavones may be due to this scission with the subsequent formation, by way of the intermediates of type (IV), of the acid-sensitive 3-aroylcoumarones of type (V).


(VII)


(VIII)


(IX)


(X)


(XI)

Those flavones which undergo demethylation by hydriodic acid with concomitant rearrangement can be demethylated without structural changes by aluminium chloride (cf., *e.g.*, Narasimhachari, Row, and Seshadri, *Proc. Indian Acad. Sci.*, 1952, **35**, *A*, 46) and

it is worthy of note that the isomerisation of 5 : 7 : 2′-trimethoxy-8-methyl*iso*flavone occurs with both of these reagents.*

This isomerisation in the *iso*flavone series has been independently observed by Professor W. Baker, F.R.S., and his colleagues (personal communications and *Chem. and Ind.*, 1953, 277).

We previously suggested that the stability of a number of 2-hydroxy*iso*flavanones might be ascribed, at least in part, to the stabilisation of the system by hydrogen bonding as in (XI). The preparation of further 2-hydroxy-2′-methoxy*iso*flavanones of type (XI) is described in the Experimental section; their formulation as 2-hydroxy*iso*flavanones rather than as *iso*flavones containing a molecule of water of crystallisation rests upon the arguments previously advanced (Whalley, *loc. cit.*) and is substantiated by a comparison of the ultra-violet absorption spectra. Our repeated attempts to obtain *iso*flavanones from deoxybenzoins lacking the 2′-methoxyl group have provided only ill-defined products, but Professor W. Baker (personal communication) informs us that he has obtained 2-hydroxy-*iso*flavanones from deoxybenzoins which do not possess 2′-methoxyl groups, and hence whilst the presence of the 2′-group might well enhance the stability of 2-hydroxy*iso*-flavanones it is apparently not necessary for the production of this system.

The 2′-methoxy*iso*flavones described in this paper are resinified very readily by hydriodic acid, even on use of the modified technique now detailed; in particular 7 : 2′-dimethoxy*iso*flavone is extremely sensitive.

Experimental

5 : 7 : 2′-*Trihydroxy*iso*flavone* (I; R = H).—(*a*) A solution of 5 : 7 : 2′-trimethoxy*iso*flavone (Whalley, *loc. cit.*) (2·5 g.) in benzene (50 ml.) containing powdered aluminium chloride (6 g.) was heated on the steam-bath during 5 hr. The cooled mixture was decomposed by ice and excess of 2N-hydrochloric acid, and the sticky precipitate collected, dried, and extracted with hot benzene. The insoluble residue (0·5 g.) separated from aqueous methanol in colourless needles, m. p. 224°, unchanged on sublimation and having a violet ferric reaction in alcohol. Two subsequent recyclisations of the partially demethylated *iso*flavones contained in the benzene extracts furnished a further 0·5 g. of 5 : 7 : 2′-trihydroxy*iso*flavone (Found: C, 66·9; H, 3·7. Calc. for $C_{15}H_{10}O_5$: C, 66·7; H, 3·7%).

(*b*) 5 : 7 : 2′-Trimethoxy*iso*flavone (1·5 g.) in hydriodic acid (*d* 1·7; 50 ml.) containing a little "phosphorous acids" was refluxed during 45 min. (demethylation was incomplete if shorter times were employed), then cooled, and the sticky solid collected, washed, dried, and sublimed, giving 5 : 7 : 2′-trihydroxy*iso*flavone (0·1 g.), m. p. 224°, identical with the product from (*a*) and converted quantitatively by methyl sulphate and anhydrous potassium carbonate in boiling acetone into 5 : 7 : 2′-trimethoxy*iso*flavone.

Demethylation of 5 : 7 : 2′-*Trimethoxy*-8-*methyl*iso*flavone*.—(*a*) 5 : 7 : 2′-Trimethoxy-8-methyl-*iso*flavone (Whalley, *loc. cit.*) (2 g.) in hydriodic acid (*d* 1·7; 100 ml.) containing "phosphorous acids" was refluxed for 45 min. (needed for complete demethylation). After isolation the semi-crystalline mass was purified from aqueous methanol, to give a very difficultly separable mixture of 5 : 7 : 2′-trihydroxy-8-methyl- and of 5 : 7 : 2′-trihydroxy-6-methyl-*iso*flavone, in very pale buff-coloured needles, m. p. 200—245° (Found: C, 67·8; H, 4·7. Calc. for $C_{16}H_{12}O_5$: C, 67·6; H, 4·3%). Methylation of this mixture by methyl sulphate–potassium carbonate–acetone during 50 hr. furnished a crystalline product, purified from methanol, gave 5 : 7 : 2′-*trimethoxy*-6-*methyl*iso*flavone* (0·2 g.), needles, m. p. 220°, having a negative ferric reaction in alcohol, dissolving in concentrated sulphuric acid to a pale yellow solution, unchanged on warming, and subliming at 200°/0·1 mm. without change in m. p. [Found: C, 69·9; H, 5·7; OMe, 28·2. $C_{16}H_9O_2(OMe)_3$ requires C, 69·9; H, 5·6; OMe, 28·5%]. This was identical with a synthetic specimen. Concentration of the methanolic mother-liquors furnished a second product, which after purification from ethyl acetate gave 5 : 7 : 2′-trimethoxy-8-methyl*iso*flavone (0·2 g.), m. p. and mixed m. p. 180°.

(*b*) Demethylation of 5 : 7 : 2′-trimethoxy-8-methyl*iso*flavone (1 g.) in benzene (25 ml.)

* [*Note added*, 16.7.53.] Since the preparation of this paper Donnelly, Philbin, and Wheeler (*Chem. and Ind.*, 1953, 567) have suggested that, as no rearrangement has yet been observed during demethylation of 5 : 8-dimethoxyflavones by aluminium chloride, the production of some 5 : 7 : 2′-trihydroxy-6-methyl*iso*flavone from 5 : 7 : 2′-trimethoxy-8-methyl*iso*flavone by this reagent might be ascribed to the direct migration of the methyl residue rather than to ring opening followed by ring closure in an alternative position.

containing powdered aluminium chloride (3 g.) on the steam-bath during 2½ hr. furnished a product (0·8 g.) which, after purification from aqueous methanol and subsequent complete methylation, was separated into 5 : 7 : 2′-trimethoxy-8- (0·3 g.) and 5 : 7 : 2′-trimethoxy-6-methyl*iso*flavone (0·3 g.).

5 : 7 : 2′-*Trimethoxy*-6-*methyl*iso*flavone* (III; R = R′ = Me).—5 : 7 : 2′-Trihydroxy*iso*flavone (1·5 g.) in methanol (50 ml.) containing dissolved sodium (2 g.) and methyl iodide (10 ml.) was refluxed for 15 hr. Purification of the product from methanol gave 5-*hydroxy*-7 : 2′-*dimethoxy*-6-*methyl*iso*flavone* (0·5 g.) in very pale yellow prisms, m. p. 155°, exhibiting an intense green ferric reaction in alcohol and moderately soluble in alcohol and methanol [Found: C, 69·6; H, 5·7; OMe, 18·9. $C_{16}H_{10}O_3(OMe)_2$ requires C, 69·2; H, 5·1; OMe, 19·8%].

Further methylation during 60 hr. by methyl sulphate–potassium carbonate–acetone gave a quantitative yield of 5 : 7 : 2′-trimethoxy-6-methyl*iso*flavone, m. p. 220° (Found: C, 70·4; H, 5·7; OMe, 27·5%).

The last-mentioned *iso*flavone (0·7 g.) in methanol (15 ml.) and water (10 ml.) containing sodium hydroxide (2 g.) was refluxed for 1½ hr.; acidification of the cooled hydrolysate furnished 2-*hydroxy*-4 : 6 : 2′-*trimethoxy*-5-*methyldeoxybenzoin* (0·5 g.), prisms (from methanol), m. p. 134°, having an intense olive-green ferric reaction in alcohol (Found: C, 68·6; H, 6·5. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·4%). With ethyl iodide and potassium carbonate in boiling acetone during 6 hr. this gave quantitatively 2-*ethoxy*-4 : 6 : 2′-*trimethoxy*-5-*methyldeoxybenzoin*, plates (from methanol), m. p. 89°, having a negative ferric reaction in alcohol and identical with a synthetic specimen (Found: C, 69·9; H, 6·7. $C_{20}H_{24}O_5$ requires C, 69·8; H, 7·0%).

2-*Ethoxy*-4 : 6 : 2′-*trimethoxy*-5-*methyldeoxybenzoin* (VI; R = Me).—A solution of 4-ethoxy-2 : 6-dihydroxytoluene (Herzig and Eisenstein, *Monatsh.*, 1902, **23**, 565) (2 g.) and *o*-methoxybenzyl cyanide (2 g.) in ether (75 ml.) containing zinc chloride (2 g.) was saturated at 0° with hydrogen chloride. 24 Hr. later the semicrystalline ketimine salt was separated and hydrolysed with water (50 ml.) on the steam-bath during 1 hr. Purification of the crystalline ketone from methanol gave 2-*ethoxy*-4 : 6-*dihydroxy*-2′-*methoxy*-5-*methyldeoxybenzoin* (1·2 g.) in needles, m. p. 185°, having an intense red-violet ferric reaction in alcohol (Found: C, 68·7; H, 6·3. $C_{18}H_{20}O_5$ requires C, 68·4; H, 6·4%).

Methylation by methyl sulphate, etc., furnished quantitatively 2-ethoxy-4 : 6 : 2′-trimethoxy-5-methyldeoxybenzoin, plates (from methanol), m. p. 89°, having a negative ferric reaction in alcohol.

2′-*Ethoxy*-2 : 4 : 6-*trimethoxy*-3-*methyldeoxybenzoin* (VIII; R = Me, R′ = Et).—Prepared from *o*-ethoxybenzaldehyde (47 g.) (Perkin, *Annalen*, 1868, **145**, 306) in the usual manner the *azlactone* (60 g.) separated from ethanol in bright yellow needles, m. p. 182° (Found: N, 4·7. $C_{18}H_{15}O_3N$ requires N, 4·7%). After hydrolysis of this (60 g.) the crude *o*-ethoxyphenylpyruvic acid was converted into the *oxime* (15 g.) which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) in needles, m. p. 164—165° (Found: N, 6·1. $C_{11}H_{13}O_4N$ requires N, 6·3%). Dehydration of this oxime (16 g.) with acetic anhydride furnished *o-ethoxybenzyl cyanide* (5·4 g.) as almost colourless prisms [from light petroleum (b. p. 40—60°)], m. p. 42° (Found: N, 7·9. $C_{10}H_{11}ON$ requires N, 8·7%).

The Hoesch reaction of *C*-methylphloroglucinol (5 g.) and *o*-ethoxybenzyl cyanide (5 g.) furnished 2′-*ethoxy*-2 : 4 : 6-*trihydroxy*-3-*methyldeoxybenzoin* (1 g.), needles (from benzene–methanol), m. p. 174°, having an intense violet ferric reaction in alcohol (Found: C, 68·0; H, 6·0. $C_{17}H_{18}O_5$ requires C, 67·5; H, 6·0%), giving with methyl sulphate, etc., the *trimethyl ether* (VIII; R = Me, R′ = Et), tablets (from aqueous methanol), m. p. 88°, having a negative ferric reaction in alcohol (Found: C, 69·8; H, 7·2. $C_{20}H_{24}O_5$ requires C, 69·8; H, 7·0%). The mixed m. p. with the isomeric 2-ethoxy-4 : 6 : 2′-trimethoxy-5-methyldeoxybenzoin was *ca.* 70°.

Demethylation of 5 : 7 : 4′-*Trimethoxy*-8-*methyl*iso*flavone* (IX; R = R′ = Me).—A solution of 5 : 7 : 4′-trimethoxy-8-methyl*iso*flavone (4·5 g.) in hydriodic acid (*d* 1·7; 75 ml.) was refluxed during 12 hr., then diluted with water, and the crystalline precipitate purified from aqueous methanol to furnish 5 : 7 : 4′-trihydroxy-8-methyl*iso*flavone (3·5 g.), m. p. 252° (Whalley, *loc. cit.*). On evaporation the methanolic mother-liquors deposited crystals, m. p. *ca.* 200° (0·5 g.), which, after repeated crystallisation, had m. p. 274°, undepressed on admixture with authentic 5 : 7 : 4′-trihydroxy-6-methyl*iso*flavone. Methylation of this product during 24 hr. by the methyl sulphate method gave 5 : 7 : 4′-trimethoxy-6-methyl*iso*flavone (0·2 g.) as prisms (from methanol), m. p. 169°, identical with a specimen prepared by the methylation during 50 hr. of 5-hydroxy-7 : 4′-dimethoxy-6-methyl*iso*flavone (Whalley; Baker and Robinson, *locc. cit.*) (Found: C, 69·8; H, 5·4; OMe, 28·2%).

*5-Hydroxy-7 : 4′-dimethoxy-8-methyl*iso*flavone* (IX; R = Me, R′ = H).—Methylation of 5 : 7 : 4′-trihydroxy-8-methyl*iso*flavone (Whalley, *loc. cit.*) during 2 hr. by methyl sulphate, etc., gave quantitatively *5-hydroxy-7 : 4′-dimethoxy-8-methyl*iso*flavone* which separated from a large volume of methanol in needles, m. p. 167°, having an intense green ferric reaction in alcohol [Found: C, 69·5; H, 5·3; OMe, 19·8. $C_{16}H_{10}O_3(OMe)_2$ requires C, 69·2; H, 5·2; OMe, 19·3%].

*7 : 2′-Dimethoxy*iso*flavone.*—Prepared by a Hoesch reaction from resorcinol (6 g.) and *o*-methoxybenzyl cyanide (5 g.), *2 : 4-dihydroxy-2′-methoxydeoxybenzoin* (2 g.) separated from aqueous methanol or benzene in prisms, m. p. 164°, very soluble in methanol and ethanol and having an intense red-brown ferric reaction in alcohol (Found: C, 70·2; H, 5·7. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·5%).

Methylation by methyl iodide and potassium carbonate in boiling acetone during 1½ hr. gave quantitatively *2-hydroxy-4 : 2′-dimethoxydeoxybenzoin*, prisms (from methanol), m. p. 94°, having an intense red-brown ferric reaction in alcohol (Found: C, 69·9; H, 5·9. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

Cyclisation of this ketone (2 g.) in methyl formate solution (25 ml.) containing sodium dust (1 g.), during 24 hr. at 0°, decomposition by iced water, and crystallisation from ethyl acetate–hexane gave *2-hydroxy-7 : 2′-dimethoxy*iso*flavanone* (1·5 g.) as prisms, m. p. 134°, very easily soluble in ethanol, insoluble in cold 2N-sodium hydroxide, and having a negative ferric reaction in alcohol (Found: C, 68·1; H, 5·5. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%).

The foregoing compound (1·2 g.) was refluxed with acetic acid (5 ml.) during 30 min. Dilution with water gave quantitatively *7 : 2′-dimethoxy*iso*flavone*, needles (from aqueous methanol), m. p. 109° (Found: C, 72·4; H, 5·2. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%). In boiling hydriodic acid (*d* 1·7; 50 ml.), containing "phosphorous acid" (20 min.) this (1·0 g.) gave only an intractable red gum.

*5 : 7 : 2′ : 4′-Tetramethoxy*iso*flavone.*—2-Hydroxy-4 : 6 : 2′ : 4′-tetramethoxydeoxybenzoin (King and Neill, *J.*, 1952, 4752) (3 g.) in ethyl formate (40 ml.) containing sodium (3 g.) furnished, in the usual manner, *2-hydroxy-5 : 7 : 2′ : 4′-tetramethoxy*iso*flavanone* (2 g.) as needles (from ethyl acetate) m. p. 178° (decomp.) (Found: C, 63·2; H, 5·8. $C_{19}H_{20}O_7$ requires C, 63·3; H, 5·6%), insoluble in cold 2N-sodium hydroxide, very sparingly soluble in methanol and ethanol, and having a negative ferric reaction in alcohol.

Boiling acetic acid converted it quantitatively into 5 : 7 : 2′ : 4′-tetramethoxy*iso*flavone, m. p. 204° (Found: C, 66·7; H, 5·7. Calc. for $C_{19}H_{18}O_6$: C, 66·7; H, 5·3%) (King and Neill, *loc. cit.*, record m. p. 203—204°). Demethylation of this *iso*flavone, even under the most favourable conditions, with hydriodic acid furnished a resin from which only traces of crystalline material could be isolated.

*5 : 7 : 2′ : 3′-Tetramethoxy-8-methyl*iso*flavone.*—Prepared from a solution of *C*-methylphloroglucinol (5 g.) and 2 : 3-dimethoxybenzyl cyanide (5 g.) in ether (150 ml.) containing zinc chloride (4 g.) *2 : 4 : 6-trihydroxy-2′ : 3′-dimethoxy-3-methyldeoxybenzoin* (4·2 g.) separated from aqueous methanol in almost colourless prisms, m. p. 201°, having an intense violet ferric reaction in alcohol (Found: C, 64·1; H, 5·9. $C_{17}H_{18}O_6$ requires C, 64·2; H, 5·7%).

Methylation of this (2 g.) by methyl sulphate, etc., furnished *2-hydroxy-4 : 6 : 2′ : 3′-tetramethoxy-3-methyldeoxybenzoin* (1·5 g.) in prisms, m. p. 160° (from ethyl acetate), exhibiting a red-brown ferric reaction in alcohol (Found: C, 66·2; H, 6·4. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%).

Cyclisation in the usual way furnished *2-hydroxy-5 : 7 : 2′ : 3′-tetramethoxy-8-methyl*iso*flavanone* (1·5 g. from 2 g.) as tablets, m. p. 178° (decomp.), from methanol or needles, m. p. 178° (decomp.), from ethyl acetate (Found: C, 64·2; H, 6·2. $C_{20}H_{22}O_7$ requires C, 64·2; H, 5·9%). It was moderately soluble in methanol, ethanol, and ethyl acetate but insoluble in cold 2N-sodium hydroxide and had a negative ferric reaction in alcohol.

The foregoing *iso*flavanone was converted rapidly and quantitatively into *5 : 7 : 2′ : 3′-tetramethoxy-8-methyl*iso*flavone* in boiling acetic acid and separated from aqueous acetone or aqueous alcohol in needles, m. p. 141°, readily soluble in methanol, ethanol, and ethyl acetate and having a negative ferric reaction in alcohol (Found: C, 67·5; H, 5·3. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·7%).

*5 : 7 : 2′ : 3′-Tetramethoxy*iso*flavone.*—Prepared from phloroglucinol (6 g.) and 2′ : 3′-dimethoxybenzyl cyanide (6 g.) in the usual manner, *2 : 4 : 6-trihydroxy-2′ : 3′-dimethoxydeoxybenzoin* (4·5 g.) separated from aqueous methanol in almost colourless plates, m. p. 193°, having an intense violet ferric reaction in alcohol (Found: C, 63·3; H, 5·6. $C_{18}H_{16}O_6$ requires C, 63·2; H, 5·3%). Methylation by methyl sulphate, etc., furnished *2-hydroxy-4 : 6 : 2′ : 3′-*

tetramethoxydeoxybenzoin (4 g. from 4 g.) as prisms, m. p. 132° (from methanol–acetone), having an intense violet ferric reaction in alcohol (Found : C, 64·7; H, 6·1. $C_{18}H_{20}O_6$ requires C, 65·1; H, 6·1%).

Cyclisation with ethyl formate in the usual way gave 2-*hydroxy*-5 : 7 : 2′ : 3′-*tetramethoxy*iso*flavanone* (2 g. from 4 g.) as prisms, m. p. 191—192° (decomp.) (from ethanol), insoluble in 2N-sodium hydroxide, sparingly soluble in methanol and ethanol, having a negative ferric reaction in alcohol, and decomposing on sublimation at 0·001 mm. (Found : C, 63·4; H, 5·9. $C_{19}H_{20}O_7$ requires C, 63·3; H, 5·6%).

Prepared from the foregoing *iso*flavanone in refluxing acetic acid, 5 : 7 : 2′ : 3′-*tetramethoxy*-iso*flavone* separated from aqueous acetic acid in prisms, m. p. 178° [Found : C, 66·7; H, 5·5; OMe, 36·5. $C_{15}H_6O_2(OMe)_4$ requires C, 66·7; H, 5·3; OMe, 36·3%].

The author thanks Smith, Kline, and French Laboratories, Philadelphia, for gifts of *C*-methylphloroglucinol and 2 : 3-dimethoxybenzaldehyde and for the hospitality of their laboratories where part of this work was performed. The microanalyses were by Mrs. Rita Preis, Miss Doris Aitkin, and Miss Sally Haws. The absorption spectra were determined in methanol solution using a Carey self-recording spectrophotometer, model 11 M.

UNIVERSITY OF LIVERPOOL. [*Received, June 20th,* 1953.]

676. *Fluoro-olefins. Part II.* Synthesis and Reactions of Some 3 : 3 : 3-Trihalogenopropenes.*

By R. N. HASZELDINE.

The synthesis of the olefins $CX_3{\cdot}CY{:}CH_2$ (CX_3 = $CClF_2$ or CF_3; Y = H, Cl, or Br) from 3-bromo-1 : 1 : 1-trichloropropane, 1 : 1 : 1 : 3-tetrachloropropane, or 3 : 3 : 3-trichloropropene, is described. Reaction of the compounds $CX_3{\cdot}CH_2{\cdot}CH_2Y$ or $CX_3{\cdot}CHY'{\cdot}CH_2Y$ (CX_3 = CCl_3 or $CBrCl_2$; Y and Y′ = Cl or Br) with antimony trifluoride yields $CF_3{\cdot}CH_2{\cdot}CH_2Y$ or $CF_3{\cdot}CHY'{\cdot}CH_2Y$.

The allylic rearrangement of $CCl_3{\cdot}CH{:}CH_2$ and $CCl_3{\cdot}CCl{:}CH_2$ to $CCl_2{:}CH{\cdot}CH_2Cl$ or $CCl_2{:}CCl{\cdot}CH_2Cl$ takes place on heating, or in presence of strong acids or Friedel–Crafts catalysts. $CClF_2{\cdot}CH{:}CH_2$ probably rearranges to $CF_2{:}CH{\cdot}CH_2Cl$.

THIS communication describes the synthesis of compounds of the type $CX_3{\cdot}CY{:}CH_2$ (CX_3 = $CClF_2$ or CF_3; Y = H, Cl, or Br) required for experiments involving 3 : 3 : 3-trifluoro-propene and -propyne reported in other series (*J.*, 1951, 2495; 1952, 2504).

The starting compounds were 1 : 1 : 1 : 3-tetrachloropropane and 3-bromo-1 : 1 : 1-trichloropropane, prepared by the benzoyl peroxide-initiated reaction of carbon tetrachloride or bromotrichloromethane with ethylene (Joyce, Hanford, and Harmon, *J. Amer. Chem. Soc.*, 1948, **70**, 2529; Kharasch, Reinmuth, and Urry, *ibid.*, 1947, **69**, 1105).

The tetrachloropropane was converted into 3-chloro-1 : 1 : 1-trifluoropropane in high yield on treatment with antimony trifluoride activated by quinquevalent antimony, with benzotrifluoride or ethylene dichloride as diluent (cf. Henne and Nager, *ibid.*, 1951, **73**, 1042, Stewart and Henne, unpublished); small amounts of 1 : 3-dichloro-1 : 1-difluoropropane were also isolated.

Dehydrochlorination of 1 : 1 : 1 : 3-tetrachloropropane gave three products (I)—(III) :

$$CCl_3{\cdot}CH_2{\cdot}CH_2Cl \xrightarrow{KOH\text{–}EtOH} \underset{(I)}{CCl_3{\cdot}CH{:}CH_2} + \underset{(II)}{CCl_2{:}CH{\cdot}CH_2Cl} + \underset{(III)}{CCl_2{:}CH{\cdot}CH_2{\cdot}OEt}$$

Compound (I), b. p. 100·5°, was prepared by Ladd and Slunkle (U.S.P. 2,561,516/1951) and by Nesmeyanov, Freidlina, and Firstov (*Doklady Akad. Nauk. S.S.S.R.*, 1951, **78**, 717; *Chem. Abs.*, 1952, **46**, 1957), and compound (II), b. p. 130·5°, was prepared by Kirrman and Kremer (*Bull. Soc. chim.*, 1948, **15**, 166). The constitution of (I) is proved below, and the boiling points of the known trichloropropenes now fall into the expected order : $CH_2Cl{\cdot}CCl{:}CHCl$, 142°; $CH_2Cl{\cdot}CH{:}CCl_2$, 131°; $CH_3{\cdot}CCl{:}CCl_2$, 116°; $CCl_3{\cdot}CH{:}CH_2$, 101°. The ether (III) has also been prepared by reaction of sodium ethoxide with (II). In

* Part I, *J.*, 1952, 4423.

3 : 3 : 3-trichloropropene nucleophilic attack on the $:CH_2$ group is facilitated by the inductive effect of the CCl_3 group :

$$EtO^- \curvearrowright CH_2{:}CH{-}CCl_2{-}Cl \curvearrowright \longrightarrow EtO{\cdot}CH_2{\cdot}CH{:}CCl_2 + Cl^-$$

The ready replacement of allylic chlorine by fluorine (Swarts, *Bull. Acad. roy. Belg.*, 1898, **35**, 375; 1920, **78**, 389) is further exemplified by the conversion of 3 : 3 : 3-trichloropropene into 3 : 3 : 3-trifluoropropene. Completely anhydrous conditions must be employed, however, since moisture liberates acid which converts (I) into (II). Anhydrous antimony trifluoride catalyses this allylic rearrangement only slowly. The change (I) $\longrightarrow$ (II) is brought about by concentrated acids, by ferric or aluminium chloride, or by heat (see also Nesmeyanov *et al.*, *loc. cit.*). Ethanolic potassium hydroxide has little effect in absence of chloride, and hydrogen fluoride gives mainly tar, although some halogen replacement occurs. Reaction of (II) with antimony trifluoride gave only complex products. Henne and Whaley (*J. Amer. Chem. Soc.*, 1942, **64**, 1157) reported that 3 : 3 : 3-trichloropropene failed to react with antimony trifluoride, but their starting material was probably 1 : 1 : 2-trichloropropene. Whaley and Davis (*ibid.*, 1948, **70**, 1026) observed allylic rearrangement on treatment of 1 : 1 : 2 : 3 : 3-pentachloropropene with antimony trifluoride, $CHCl_2{\cdot}CCl{:}CCl_2 \longrightarrow CHF_2{\cdot}CCl{:}CCl_2 + CF_3{\cdot}CCl{:}CHCl + CF_2Cl{\cdot}CCl{:}CHCl$, although the compound $CCl_3{\cdot}CCl{:}CHCl$ apparently yielded only $CF_3{\cdot}CCl{:}CHCl$. It is to be noted that other compounds reported to undergo replacement of allylic halogen by fluorine with high yields would give the same product even if rearrangement had occurred (*e.g.*, $CCl_3{\cdot}CCl{:}CCl_2$, $CF_2Cl{\cdot}CCl{:}CF_2$, $CCl_3{\cdot}CH{:}CCl_2$).

The following reactions have been applied to 3 : 3 : 3-trichloropropene :

$$CCl_3{\cdot}CH{:}CH_2 \xrightarrow{Cl_2} CCl_3{\cdot}CHCl{\cdot}CH_2Cl \xrightarrow{SbF_3Cl_2} CF_3{\cdot}CHCl{\cdot}CH_2Cl \xrightarrow{Zn\text{-}EtOH} CF_3{\cdot}CH{:}CH_2$$
$$\text{(IV)}$$

$$\text{(IV)} \xrightarrow{KOH\text{-}EtOH} CCl_3{\cdot}CCl{:}CH_2 \ (\text{VI}) + CCl_2{:}CCl{\cdot}CH_2Cl \ (\text{VII})$$

$$CCl_3{\cdot}CH{:}CH_2 \xrightarrow{Br_2} CCl_3{\cdot}CHBr{\cdot}CH_2Br \xrightarrow{SbF_3Cl_2} CF_3{\cdot}CHBr{\cdot}CH_2Br$$
$$\text{(V)}$$

$$\text{(V)} \xrightarrow{KOH\text{-}EtOH} CCl_3{\cdot}CBr{:}CH_2$$

$$CCl_3{\cdot}CX{:}CH_2 \xrightarrow{SbF_3Cl_2} CF_3{\cdot}CX{:}CH_2 \quad (X = Cl \text{ or } Br)$$

The trichloropropenes (I) and (II) react with chlorine (Nesmeyanov *et al.*, *loc. cit.*) to give the same pentachloro-compound (IV), which with antimony trifluoride yields the known 2 : 3-dichloro-1 : 1 : 1-trifluoropropane; the constitution of (IV) is thus proved. The markedly more rapid reaction of chlorine with (I) than with (II) is in accord with the proposed constitutions of (I) and (II).

The constitution of (V) follows from its conversion into the known 2 : 3-dibromo-1 : 1 : 1-trifluoropropane. The trichloropropene (II) gives, less readily, a different liquid dibromide, which in turn yields 2-bromo-3-chloro-1 : 1 : 1-trifluoropropane; this is different from the known 3-bromo-3-chloro-1 : 1 : 1-trifluoropropane. Since one bromine atom in the dibromide of (II) has been replaced by fluorine, the following reactions must have occurred :

$$CCl_2{:}CH{\cdot}CH_2Cl \xrightarrow{Br_2} CBrCl_2{\cdot}CHBr{\cdot}CH_2Cl \xrightarrow{SbF_3Cl_2} CF_3{\cdot}CHBr{\cdot}CH_2Cl$$

and the relation between (I) and (II) is proved.

With ethanolic potassium hydroxide the pentachloropropane (IV) gives two isomeric products (VI) and (VII). That the major product (VI) is 2 : 3 : 3 : 3-tetrachloropropene follows from its conversion by antimony trifluoride into the known 2-chloro-3 : 3 : 3-trifluoropropene; (VII) is 1 : 1 : 2 : 3-tetrachloropropene, since by reaction with chlorine it gives the same compound as (VI) :

$$CCl_3{\cdot}CCl{:}CH_2 \text{ or } CCl_2{:}CCl{\cdot}CH_2Cl \xrightarrow{Cl_2} CCl_3{\cdot}CCl_2{\cdot}CH_2Cl$$

Allylic rearrangement of 2 : 3 : 3 : 3-tetrachloropropene into (VII) can be brought about by heat or by addition of aluminium chloride [cf. (I) ⟶ (II), above].

The allylic chlorine atoms in 2-bromo-3 : 3 : 3-trichloropropene were similarly readily replaced by fluorine.

When 3-bromo-1 : 1 : 1-trichloropropane was treated with antimony trifluoride activated by chlorine, 3-bromo-1 : 1 : 1-trifluoropropane, 3-bromo-1-chloro-1 : 1-difluoropropane, and a compound *A* were produced. The first of these is known; the constitution of the second follows from the reactions

$$CClF_2{\cdot}CH_2{\cdot}CH_2Br \xrightarrow{KOH\text{-}EtOH} CClF_2{\cdot}CH{:}CH_2\ (VIII) \xrightarrow{SbF_3Cl_2} CF_3{\cdot}CH{:}CH_2$$

1 : 3-Dichloro-1 : 1-difluoropropane is similarly converted into (VIII).

Compound *A*, $C_3H_3BrCl_2F_2$, is formed in much lower yield when bromine is used to activate the antimony trifluoride. It boils in the region expected for a compound of this formula, and infra-red spectroscopic examination shows that it is not olefinic. Its constitution is shown by the following reactions which, since they take place in high yield, show that *A* is not a mixture of isomers. Zinc and ethanol removed equimolar amounts of bromine and chlorine, to give 3-chloro-3 : 3-difluoropropene (VIII) and 1 : 1-difluoroprop-1-ene (IX); zinc and acetic acid gave the same compounds but with increased yields of the difluoropropene. The mechanism of formation of (IX) is discussed below; its constitution is proved by its boiling point, by formation of a dichloride, b. p. 70° [cf. $CH_3{\cdot}CHCl{\cdot}CClF_2$, b. p. 69·8°; $CClF_2{\cdot}CH_2{\cdot}CH_2Cl$, 80·8°; $CH_3{\cdot}CF_2{\cdot}CHCl_2$, 79°; $CH_2Cl{\cdot}CF_2{\cdot}CH_2Cl$, 96·1°], and by its infra-red spectrum which shows the characteristic $CH{:}CF_2$ double bond stretching vibration at 5·67 μ.

Reaction of *A* with ethanolic potassium hydroxide gave an olefin $C_3H_2BrClF_2$ by removal of the elements of hydrogen chloride; bromide was not liberated. This olefin (X) reacted with antimony trifluoride to yield the known 2-bromo-3 : 3 : 3-trifluoropropene (XI). *A* is thus 2-bromo-1 : 3-dichloro-1 : 1-difluoropropane (XII):

$$\underset{(IX)}{CF_2{:}CH{\cdot}CH_3} \qquad \underset{(XII)}{CClF_2{\cdot}CHBr{\cdot}CH_2Cl} \xrightarrow{KOH\text{-}EtOH} \underset{(X)}{CClF_2{\cdot}CBr{:}CH_2} \xrightarrow{SbF_3Cl_2} \underset{(XI)}{CF_3{\cdot}CBr{:}CH_2}$$

A is also isolated as a by-product from the reaction of 1 : 2-dibromo-1 : 1 : 3-trichloropropane with antimony trifluoride.

The olefin (X) may also be obtained as follows:

$$(VIII) \xrightarrow{Br_2} CClF_2{\cdot}CHBr{\cdot}CH_2Br \xrightarrow{KOH\text{-}EtOH} CClF_2{\cdot}CBr{:}CH_2$$

3-Chloro-3 : 3-difluoropropene combined with chlorine to give a trichloride which, with ethanolic potassium hydroxide, yielded 2 : 3-dichloro-3 : 3-difluoropropene; the last compound was readily converted into the known 2-chloro-3 : 3 : 3-trifluoropropene. Exchange of allylic chlorine for fluorine is thus easy with $CCl_3{\cdot}CX{:}CH_2$ and $CClF_2{\cdot}CX{:}CH_2$ (X = H, Cl, or Br) provided that allylic rearrangement is not dominant.

The unexpected formation of (XII) from 3-bromo-1 : 1 : 1-trichloropropane must involve a complex reaction [*e.g.*, $CCl_3{\cdot}CH_2{\cdot}CH_2Br \longrightarrow CClF_2{\cdot}CH_2{\cdot}CH_2Br \longrightarrow CClF_2{\cdot}CH{:}CH_2 \longrightarrow CClF_2{\cdot}CHBr{\cdot}CH_2Br \longrightarrow$ (XI)].

The rearrangements, $CCl_3{\cdot}CH{:}CH_2 \longrightarrow CCl_2{:}CH{\cdot}CH_2Cl$; $CCl_3{\cdot}CCl{:}CH_2 \longrightarrow CCl_2{:}CCl{\cdot}CH_2Cl$, have been established as above, and the rearrangement $CClF_2{\cdot}CH{:}CH_2 \longrightarrow CF_2{:}CH{\cdot}CH_2Cl$ seems probable (see below). They can be brought about by a variety of reagents and various mechanisms are possible (for a review with references to kinetic work see Braude *Ann. Reports*, **1949**, **46**, 114).

The formation of 1 : 1-difluoroprop-1-ene (IX) on treatment of (XII) with zinc and ethanol also involves allylic rearrangement. It is well established that removal of halogen from adjacent carbon atoms which are also attached to hydrogen is easier than when the carbon atoms are attached to fluorine. The initial product from (XII) will thus be $CClF_2{\cdot}CH{:}CH_2$ and not $CF_2{:}CH{\cdot}CH_2Cl$, and rearrangement followed by reduction must occur when zinc chloride is present:

$$CClF_2{\cdot}CH{:}CH_2 \xrightarrow{ZnCl_2\text{-}EtOH} CF_2{:}CH{\cdot}CH_2Cl \xrightarrow{Zn\text{-}EtOH} CF_2{:}CH{\cdot}CH_3\ (IX)$$

Acetic acid as solvent facilitates the rearrangement and thus increases the yield of (IX). That replacement of allylic chlorine by hydrogen can occur is shown by the reactions

$$CCl_2{:}CH{\cdot}CH_2Cl \xrightarrow{Zn\text{–}EtOH} CCl_2{:}CH{\cdot}CH_3; \quad CCl_2{:}CCl{\cdot}CH_2Cl \xrightarrow{Zn\text{–}EtOH} CCl_2{:}CCl{\cdot}CH_3$$

A second example of allylic rearrangement followed by reduction (zinc–alcohol) is probably $CCl_3{\cdot}CHCl{\cdot}CH_2Cl \longrightarrow CCl_2{:}CCl{\cdot}CH_3$ although here the possibility of the reaction $CCl_3{\cdot}CHCl{\cdot}CH_2Cl \longrightarrow CCl_2{:}CH{\cdot}CH_2Cl$ (without rearrangement), followed by reduction, cannot be excluded with as much certainty as for (XI).

Experimental

Reaction of Carbon Tetrachloride with Ethylene.—The procedure of Joyce *et al.* (*loc. cit.*) was followed, with carbon tetrachloride (100 ml.), ethylene (50 atm.), and benzoyl peroxide (0·9 g.) in a 300-ml. autoclave. The temperature was slowly increased to 100° during 24 hr., and as the pressure dropped more ethylene was added. Distillation gave 1 : 1 : 1 : 3-tetrachloropropane (25%), b. p. 65°/30 mm., 158—159°/760 mm., n_D^{20} 1·482.

Reactions of 1 : 1 : 1 : 3-*Tetrachloropropane.*—(a) *With antimony trifluoride* (cf. Henne and Nager, *loc. cit.*). A flanged cylindrical steel vessel (4 l.) was fitted with large steel paddles and scrapers which could be rotated by a powerful motor and were capable of stirring and mixing efficiently a dense semi-solid mass. To antimony trifluoride (100 g.) and antimony trifluorodichloride (100 g.), stirred for 1 hr., was added benzotrifluoride (50 ml.), then 1 : 1 : 1 : 3-tetrachloropropane (75 g.) added dropwise during 3 hr. The temperature, which had been kept at 20—25°, was then raised to give a reflux in the steel condenser, which was attached to the flanged lid of the apparatus and led *via* rubber tubing to a trap cooled in liquid oxygen. Efficient stirring was essential for good yields. After 1 hr. the volatile contents were pumped out, collected in the liquid-oxygen trap, and distilled, to give 3-chloro-1 : 1 : 1-trifluoropropane (61%), b. p. 45—46°, n_D^{25} 1·334, and 1 : 3-dichloro-1 : 1-difluoropropane (10%), b. p. 81—81·5°, n_D^{25} 1·325 (*J.*, 1951, 2495). Ethylene dichloride may be used instead of benzotrifluoride if only 3-chloro-1 : 1 : 1-trifluoropropane is required. In other experiments the products were isolated in slightly increased yield by steam-distillation of the acidified (HCl) reaction mixture.

(b) *Dehydrochlorination* (cf. Nesmeyanov *et al.*, *loc. cit.*). To 1 : 1 : 1 : 3-tetrachloropropane (50 g.) in ethanol (25 ml.), stirred and cooled to −10°, was slowly added 10% ethanolic potassium hydroxide (10% excess). An immediate precipitate of potassium chloride was observed, and after 1 hour's stirring at >0° an excess of water was added, and the lower layer was washed with water, dried ($CaCl_2$), and distilled, to give 3 : 3 : 3-trichloropropene (57%), b. p. 60—60·5°/175 mm., 100·5—101·0°/760 mm., n_D^{20} 1·468 (Found: C, 24·8; H, 2·2. Calc. for $C_3H_3Cl_3$: C, 24·8; H, 2·1%), 1 : 1 : 3-trichloroprop-1-ene (30%), b. p. 90—91°/175 mm., 130·0—131·5°/760 mm., n_D^{20} 1·497 (Found: C, 24·6; H, 2·5. Calc. for $C_3H_3Cl_3$: C, 24·8; H, 2·1%), starting material (2%), 1 : 1-*dichloro*-3-*ethoxyprop*-1-*ene* (5%), b. p. 110—111°/205 mm., n_D^{20} 1·453 (Found: C, 38·7; H, 5·0. $C_5H_8OCl_2$ requires C, 38·7; H, 5·2%), and unidentified material of higher b. p. (5%). Kirrman and Kremer (*loc. cit.*) report b. p. 130—131°, n_D^{18} 1·4960, for 1 : 1 : 3-trichloroprop-1-ene. Reaction of this compound (2·0 g.) with an ethanolic solution containing 5% of sodium ethoxide and 5% of potassium hydroxide gave 1 : 1-dichloro-3-ethoxyprop-1-ene in 58% yield.

Reactions of 3 : 3 : 3-*Trichloropropene.*—(a) *Conversion into* 3 : 3 : 3-*trifluoropropene.* Resublimed anhydrous antimony trifluoride (30 g.) was vigorously stirred and treated with chlorine until the ratio of $SbF_3 : SbF_3Cl_2$ was 9 : 1. Dried ethylene dichloride (20 ml.) was then added dropwise (2 hr.) at −10° to −5° to a solution of 3 : 3 : 3-trichloropropene (10·0 g.) in ethylene dichloride (5 ml.). The reaction, which is smooth and easily controlled only if efficient stirring is maintained, was completed by heating to 60°. Distillation of the volatile product in a vacuum system gave 3 : 3 : 3-trifluoropropene (51%), b. p. −22° (Found: *M*, 96. Calc. for $C_3H_3F_3$: *M*, 96), identified spectroscopically.

(b) *Isomerisation.* 3 : 3 : 3-Trichloropropene (3·0 g.) was converted into 1 : 1 : 3-trichloroprop-1-ene as tabulated. 1 : 1 : 3-Trichloroprop-1-ene was not converted into 3 : 3 : 3-trichloropropene by the reagents listed. Nesmeyanov *et al.* (*loc. cit.*) report the isomerisation of 3 : 3 : 3-trichloropropene by aluminium chloride at 0° or by heat at 150°.

(c) *With chlorine and bromine.* Chlorine (5% excess) and 3 : 3 : 3-trichloropropene (3·0 g.), sealed in glass at 0°, readily gave 1 : 1 : 1 : 2 : 3-pentachloropropane (94%), b. p. 84—85°/20 mm.,

n_D^{20} 1·513 (Found: C, 16·4; H, 1·0. Calc. for $C_3H_3Cl_5$: C, 16·6; H, 1·4%). Nesmeyanov *et al.* report b. p. 64—65°/8 mm., n_D^{20} 1·5105.

Reagent	Amount	Temp.	Time (hr.)	Yield of CCl_2:CH·CH_2Cl (%)
SbF_3	0·5 g.	0°	12	12
Conc. HCl	2 drops	20	36	71
Conc. H_2SO_4	2 drops	20	36	75
$AlCl_3$	0·05 g.	−10	1	65
Heat	—	100	5	31
		(glass tube)		
		140	5	74
$FeCl_3$	0·1 g.	30	3	52
KOH–EtOH	2 ml. of 10%	0	5	<5
Anhyd. HF	5 ml.	0	2	10 *

* CF_3·CH:CH_2 and tar were also found.

The compound reported as 1 : 1 : 1 : 2 : 3-pentachloropropane (Huntress, "Organic Chlorine Compounds," Wiley, New York, 1948, p. 430) has m. p. 179°. Since this solid product was derived from what is now known to be 1 : 1 : 2-trichloroprop-1-ene, it is actually 1 : 1 : 1 : 2 : 2-pentachloropropane; the high m. p. is in accord with a molecule of this type, where the halogen atoms are concentrated on the minimum number of carbon atoms. The other known pentachloropropane is $CHCl_2$·CHCl·$CHCl_2$, b. p. 198—200°, $n_D^{16·5}$ 1·5131 (*op. cit.*, p. 849).

Bromine was similarly absorbed by 3 : 3 : 3-trichloropropene (5·0 g.) at 20°, to give 1 : 2-dibromo-3 : 3 : 3-trichloropropane (95%), b. p. 100—101°/10 mm., n_D^{20} 1·562 (Found: C, 12·1; H, 0·9. Calc. for $C_3H_3Br_2Cl_3$: C, 11·8; H, 1·0%). Nesmeyanov *et al.* (*loc. cit.*) report b. p. 76—77°/3 mm., n_D^{20} 1·5640.

The compound reported as 1 : 2-dibromo-3 : 3 : 3-trichloropropane is a solid, m. p. 210° (*op. cit.*, p. 663), but, since it was obtained from what is now known to be 1 : 1 : 2-trichloropropene, this solid is actually 1 : 2-dibromo-1 : 1 : 2-trichloropropane; a specimen prepared from authentic 1 : 1 : 2-trichloropropene had m. p. 216°.

Treatment of 1 : 2-dibromo-3 : 3 : 3-trichloropropane (4·0 g.) with a 50% excess of antimony trifluoride containing 40% of antimony trifluorodichloride at 90° for 12 hr. in a vigorously shaken steel autoclave gave 1 : 2-dibromo-3 : 3 : 3-trifluoropropane (53%), b. p. 116°, n_D^{25} 1·426 (Found: *M*, 254) (*J.*, 1951, 2495), identified spectroscopically and readily debrominated to 3 : 3 : 3-trifluoropropene (90%).

The pentachloropropane (3·1 g.) and antimony trifluoride similarly gave 1 : 2-dichloro-3 : 3 : 3-trifluoropropane (47%), b. p. 76—77° (Found: *M*, 167), identified spectroscopically and dechlorinated to 3 : 3 : 3-trifluoropropene (92%).

Ice-cold 10% ethanolic potassium hydroxide (5% excess) was added to 1 : 1 : 1 : 2 : 3-pentachloropropane (3·7 g.) at 0—5°, to give 2 : 3 : 3 : 3-tetrachloropropene (65%), b. p. 76—77°/70 mm., n_D^{20} 1·504 (Found: C, 20·2; H, 0·9. Calc. for $C_3H_2Cl_4$: C, 20·0; H, 1·1%), 1 : 1 : 2 : 3-tetrachloroprop-1-ene (10%), b. p. 92°/70 mm., n_D^{20} 1·518 (Found: C, 20·2; H, 1·1. Calc. for $C_3H_2Cl_4$: C, 20·0; H, 1·1%), and a middle fraction (15%). Hatch and McDonald (*J. Amer. Chem. Soc.*, 1952, **74**, 3328) report b. p. 59°/17 mm., 162°/743 mm., for 1 : 1 : 2 : 3-tetrachloroprop-1-ene.

1 : 2-Dibromo-3 : 3 : 3-trichloropropane (4·1 g.) similarly yielded 2-bromo-3 : 3 : 3-trichloropropene (61%), b. p. 81—82°/30 mm., n_D^{20} 1·535 (Found: C, 16·3; H, 1·0. Calc. for $C_3H_2BrCl_3$: C, 16·0; H, 0·9%), and a residue which decomposed on attempted distillation.

Reactions of 1 : 1 : 3-*Trichloroprop*-1-*ene*.—Unlike 3 : 3 : 3-trichloropropene, 1 : 1 : 3-trichloroprop-1-ene (3·7 g.) failed to react appreciably with bromine at 10° (2 hr.). After its exposure to ultra-violet light (1 hr.) in a Pyrex vessel, 1 : 2-*dibromo*-1 : 1 : 3-*trichloropropane* (66%), b. p. 105—6°/11 mm. (Found: C, 12·1; H, 1·0. $C_3H_3Br_2Cl_3$ requires C, 11·8; H, 1·0%), and unchanged olefin were isolated.

The dibromide (4·1 g.) was treated with antimony trifluoride as described above for its isomer, and gave 2-*bromo*-1-*chloro*-3 : 3 : 3-*trifluoropropane* (58%), b. p. 94—96° (Found: C, 17·0; H, 1·0%; *M*, 210. $C_3H_3BrClF_3$ requires C, 17·0; H, 1·4%; *M*, 211·5). The isomeric 1-bromo-1-chloro-3 : 3 : 3-trifluoropropane has been described (*J.*, 1951, 2495). Reaction at 50° gave as by-product 2-bromo-1 : 3-dichloro-1 : 1-difluoropropane (15%), shown by spectroscopic examination to be identical with compound *A* (see below).

Reaction of chlorine with 1 : 1 : 3-trichloroprop-1-ene (3·3 g.) was very slow in absence of light, but on exposure to radiation of wave-length >3000 Å yielded 1 : 1 : 1 : 2 : 3-penta-

chloropropane (85%), b. p. 80—81°/18 mm., shown to be identical with the compound prepared as above from 3 : 3 : 3-trichloropropene.

Reactions of 2 : 3 : 3 : 3-*Tetrachloropropene and* 2-*Bromo*-3 : 3 : 3-*trichloropropene.*—(a) *With antimony trifluoride.* Antimony trifluoride (20 g., containing 10% of SbF_3Cl_2) was slowly heated from −5° to 55° with 2 : 3 : 3 : 3-tetrachloropropene (4·1 g.) and ethylene dichloride (10 ml.), to give 2-chloro-3 : 3 : 3-trifluoropropene (59%), b. p. 15·5° (Found: *M*, 130. Calc. for $C_3H_2ClF_3$: *M*, 130·5), identical with the material prepared earlier (*J.*, 1951, 2495). 2-Bromo-3 : 3 : 3-trichloropropene (2·2 g.) similarly yielded 2-bromo-3 : 3 : 3-trifluoropropene (64%), b. p. 33—34° (Found: *M*, 175. Calc. for $C_3H_2BrF_3$: *M*, 175).

(b) *Isomerisation.* Aluminium chloride (0·1 g.) and 2 : 3 : 3 : 3-tetrachloropropene (2·0 g.), sealed at 0° for 4 hr., gave 1 : 1 : 2 : 3-tetrachloroprop-1-ene (51%), b. p. 89—90°/67 mm., n_D^{22} 1·517. This was also obtained (45%) by heating 2 : 3 : 3 : 3-tetrachloropropene (2·3 g.) at 180° for 5 hr. in a glass tube.

(c) *With chlorine.* A slight excess of chlorine combined readily with 2 : 3 : 3 : 3-tetrachloropropene (1·1 g.) at 0°, to give 1 : 1 : 1 : 2 : 2 : 3-hexachloropropane, b. p. 124—125°/40 mm. (Found: C, 14·2; H, 0·9. Calc. for $C_3H_2Cl_6$: C, 14·3; H, 0·8%). The same compound, b. p. 133—135°/60 mm., was prepared from 1 : 1 : 2 : 3-tetrachloroprop-1-ene (0·5 g.) and chlorine on exposure in a Pyrex tube to ultra-violet light (1 hr.).

Reactions of 1-*Bromo*-3 : 3 : 3-*trichloropropane.*—1-Bromo-3 : 3 : 3-trichloropropane, b. p. 97—98°/50 mm., n_D^{20} 1·513, was prepared in 60% yield from bromotrichloromethane (105 g.), ethylene (50 atm. in a 300-ml. autoclave) and benzoyl peroxide (0·8 g.), heated from 0° to 70° during 5 hr., then kept at 70° for 4 hr. before being heated to 90° for 1 hr.

(a) *Dehydrobromination.* Ice-cold ethanolic potassium hydroxide (5% excess of 10%) was added (2 hr.) to 1-bromo-3 : 3 : 3-trichloropropane (26·7 g.) in ethanol (10 ml.), with vigorous stirring at 0°. After a further hour an excess of water was added rapidly and the organic layer separated, dried ($CaCl_2$), and distilled, to give 3 : 3 : 3-trichloropropene (67%), b. p. 50—50·5°/125 mm., n_D^{20} 1·468, identical with the material described above, and a small amount of a product with higher b. p.

(b) *Reaction with antimony dichlorotrifluoride.* The apparatus described for 1 : 1 : 1 : 3-tetrachloropropane (above) was used. Antimony trifluoride (70 g.) and antimony dichlorotrifluoride (80 g.) were thoroughly mixed at 60°, then cooled to 20°. A solution of 1-bromo-3 : 3 : 3-trichloropropane (52 g.) in benzotrifluoride (20 ml.) was added (3 hr.) at 20—25° and the temperature was then raised to 60° for 30 min. Steam-distillation, etc., gave (i) 1-bromo-3 : 3 : 3-trifluoropropane (51%), b. p. 62—64°, n_D^{20} 1·360 (*J.*, 1951, 2495), identified spectroscopically, (ii) a fraction, b. p. 98—107°, which contained benzotrifluoride, (iii) 1-bromo-3-chloro-3 : 3-difluoropropane [*ca.* 15% determined by treatment of the mixture with alcoholic potassium hydroxide and separation of the olefin by distillation (see below)], and (iv) a compound *A*, (20%), b. p. 133—134°, n_D^{18} 1·448 (see below).

In a second experiment, antimony trifluoride (150 g.) was converted into dichlorotrifluoride (50%), and to it was added 1-bromo-3 : 3 : 3-trichloropropane (43·5 g.) in the absence of a solvent. Efficient stirring was essential to prevent extensive decomposition. After 3 hr. at 25°, the temperature was raised to 75° for 30 min. The products were 1-bromo-3 : 3 : 3-trifluoropropane (42%), b. p. 63—64°, 1-*bromo*-3-*chloro*-3 : 3-*difluoropropane* (11%), b. p. 99—102°, on redistillation 100—100·5°, n_D^{20} 1·362 (Found: C, 18·7; H, 2·0. $C_3H_4BrClF_2$ requires C, 18·6; H, 2·1%), and compound *A* (30%), b. p. 130—134°.

At 40°, bromotrichloropropane (46·2 g.) gave 1-bromo-3 : 3 : 3-trifluoropropane (19%), b. p. 63—65°, 1-bromo-3-chloro-3 : 3-difluoropropane (39%), b. p. 100—103°, compound *A* (10%), b. p. 132—135°, and starting material (15%). 1-Bromo-3 : 3-dichloro-3-fluoropropane was not detected.

(c) *Reaction with antimony dibromotrifluoride.* The last two experiments of (b) above were repeated, with bromine instead of chlorine to produce Sb^V salts. Treating 1-bromo-3 : 3 : 3-trichloropropane (45 g.) at +75°, and removing the products by pumping, gave 1-bromo-3 : 3 : 3-trifluoropropane (53%), b. p. 63—64°, 1-bromo-3-chloro-3 : 3-difluoropropane (27%), b. p. 99—102°, and compound *A* (7%), b. p. 132—135°. With a maximum reaction temperature of 40°, the bromotrichloropropane (45 g.) gave 1-bromo-3 : 3 : 3-trifluoropropane (26%), 1-bromo-3-chloro-3 : 3-difluoropropane (42%), and starting material (17%); compound *A* was not formed.

Dehydrobromination of 1-*Bromo*-3-*chloro*-3 : 3-*difluoropropane.*—To the compound (5·6 g.), in ethanol (5 ml.), cooled to 10°, was added dropwise (1 hr.) a 10% excess of ice-cold 10% ethanolic potassium hydroxide. Dilute hydrochloric acid was then added in excess, and

air was blown through the solution. The combined volatile products were fractionated in a vacuum-system, to give **3-*chloro*-3 : 3-*difluoropropene*** (78%), b. p. 18° (isoteniscope) (Found: C, 31·8; H, 2·5%; *M*, 113. $C_3H_3ClF_2$ requires C, 32·0; H, 2·7%; *M*, 112·5).

Dehydrochlorination of **1 : 3-*Dichloro*-1 : 1-*difluoropropane***.—The compound (3·1 g.), treated as in the last experiment, gave 3-chloro-3 : 3-trifluoropropene (84%), b. p. 17·5° (Found: *M*, 112. Calc. for $C_3H_3ClF_2$: *M*, 112·5), identical with the compound obtained above.

Constitution and Reactions of Compound A.—*A* was shown to be **2-*bromo*-1 : 3-*dichloro*-1 : 1-*difluoropropane***, b. p. 133·5—134·0°, n_D^{25} 1·444 (Found: C, 15·6; H, 1·5; Cl + Br, 51·0. $C_3H_3BrCl_2F_2$ requires C, 15·8; H, 1·3; Cl + Br, 50·6%), by the following reactions:

(a) *Dehydrochlorination*. The technique described above for 1-bromo-3-chloro-3 : 3-difluoropropane was applied to *A* (8·2 g.), to give **2-*bromo*-3-*chloro*-3 : 3-*difluoropropene*** (89%), b. p. 78·5—79·0°, n_D^{20} 1·415 (Found: C, 18·7; H, 1·3%; *M*, 191. $C_3H_2BrClF_2$ requires C, 18·8; H, 1·1%; *M*, 191·5), and unchanged *A* (5%).

The olefin (4·3 g.) was added dropwise to a stirred suspension of antimony dichlorotrifluoride (10 g.) and antimony fluoride (5 g.) in ethylene dichloride (10 ml.) at 20°, to give 2-bromo-3 : 3 : 3-trifluoropropene (85%), b. p. 33° (isoteniscope) (Found: C, 20·7; H, 1·4%; *M*, 175. Calc. for $C_3H_2BrF_3$: C, 20·6; H, 1·4%; *M*, 175), identified by its infra-red spectrum.

(b) *Dehalogenation*. (i) *In ethanol*. *A* (10·7 g.) in ethanol (20 ml.) was added dropwise (1·5 hr.) to zinc (30 g.) and refluxing ethanol (30 ml.) in a flask fitted with reflux condenser at 25°. At the end of the reaction an excess of water was added, and the flask was swept out with nitrogen. Chloride and bromide had been formed in equimolar amounts. The combined volatile products were fractionated to give (*a*) 3-chloro-3 : 3-difluoropropene (72%), b. p. 17° (Found: *M*, 112. Calc. for $C_3H_3ClF_2$: *M*, 112·5), shown by its infra-red spectrum to be identical with the material obtained above from 1-bromo-3-chloro-3 : 3-difluoropropane and 1 : 3-dichloro-3 : 3-difluoropropane, and (*b*) 1 : 1-difluoroprop-1-ene (21%), b. p. −29° (isoteniscope) (Found: C, 46·2; H, 5·2%; *M*, 78. Calc. for $C_3H_4F_2$: C, 46·2; H, 5·1%; *M*, 78). Henne and Waalkes (*J. Amer. Chem. Soc.*, 1946, **68**, 496) report b. p. −29° for 1 : 1-difluoroprop-1-ene.

Chlorine (5% excess) combined readily with 1 : 1-difluoroprop-1-ene (1·1 g.) at 0°, giving 1 : 2-dichloro-1 : 1-difluoropropane (90%), b. p. 70—70·5° (Found: *M*, 149. Calc. for $C_3H_4Cl_2F_2$: *M*, 149). Robbins (*J. Pharmacol.*, 1946, **86**, 197) reports b. p. 69·8°.

(ii) *In acetic acid*. The experiment was repeated with glacial acetic acid in place of ethanol. *A* (6·3 g.) gave 3-chloro-3 : 3-difluoropropene (41%) and 1 : 1-difluoroprop-1-ene (52%), separated in the vacuum-system and identified spectroscopically.

(c) *Reactions of* **3-*chloro*-3 : 3-*difluoropropene***. The compound (2·0 g.), treated with a slight excess of bromine in a Pyrex vessel exposed to ultra-violet light, yielded **1 : 2-*dibromo*-3-*chloro*-3 : 3-*difluoropropane*** quantitatively (Found: C, 13·0; H, 1·0. $C_3H_3Br_2ClF_2$ requires C, 13·2; H, 1·1%), b. p. 151—152°, n_D^{21} 1·474. The dibromide (3·1 g.) with ethanolic potassium hydroxide at 0° gave 2-bromo-3-chloro-3 : 3-difluoropropene (89%), b. p. 78·5°, n_D^{20} 1·415 (Found: *M*, 190. Calc. for $C_3H_2BrClF_2$: *M*, 191·5), shown by infra-red spectroscopic examination to be identical with the compound obtained by dehydrochlorination of *A*.

Chlorine (slight excess) combined with 3-chloro-3 : 3-difluoropropene (3·1 g.) at 0° on exposure to ultra-violet light and gave **1 : 2 : 3-*trichloro*-1 : 1-*difluoropropane*** (98%), b. p. 113°, n_D^{20} 1·415 (Found: C, 19·8; H, 1·6%; *M*, 185. $C_3H_3Cl_3F_2$ requires C, 19·6; H, 1·6%; *M*, 183·5). The trichloride (4·1 g.), treated with ethanolic potassium hydroxide at 0°, gave **2 : 3-*dichloro*-3 : 3-*difluoropropene*** (91%), b. p. 57—58°, n_D^{22} 1·378 (Found: C, 24·7; H, 1·5%; *M*, 147. $C_3H_2Cl_2F_2$ requires C, 24·5; H, 1·4%; *M*, 147).

The last compound (1·75 g.) was sealed with a 1 : 1 mixture of SbF_3 and SbF_3Cl_2 and set aside at 30° for 1 hr. Fractionation *in vacuo* then gave 2-chloro-3 : 3 : 3-trifluoropropene (81%), b. p. 15° (Found: *M*, 131. Calc. for $C_3H_2ClF_3$: *M*, 130·5), identical with the material described earlier (*J.*, 1951, 2495).

Reaction of Chloro-compounds with Zinc and Ethanol.—(a) **1 : 1 : 3-*Trichloroprop*-1-*ene***. The compound (5·1 g.) was added (1 hr.) to stirred zinc (10 g.) and 95% ethanol (20 ml.) at 65°. Filtration and addition of an excess of water gave an organic layer which, dried ($CaCl_2$) and distilled, gave 1 : 1-dichloroprop-1-ene (51%), b. p. 76—77°, n_D^{20} 1·445. Kirrman and Oestermann (*loc. cit.*) report b. p. 76·5°, n_D^{18} 1·4465. The olefin was identified by its infra-red spectrum, and by formation at 0° of a dichloride, b. p. 95°/120 mm., 155° (micro), n_D^{20} 1·487. Huntress (*op. cit.*, p. 757) records b. p. 153°.

(b) **1 : 1 : 2 : 3-*Tetrachloroprop*-1-*ene***. This compound (4·6 g.) was treated as above and yielded 1 : 1 : 2-trichloroprop-1-ene (53%), b. p. 116°, n_D^{20} 1·481. Kirrman and Oestermann

report b. p. 41°/52 mm. The olefin and bromine gave 1 : 2-dibromo-1 : 1 : 2-trichloropropane m. p. 216°.

(c) 1 : 1 : 1 : 2 : 3-*Pentachloropropane.* Treatment of this compound (2·1 g.) with zinc and 95% ethanol at 65° gave 1 : 1-dichloroprop-1-ene (58%), b. p. 75—77°, identified spectroscopically, and unidentified material of higher b. p.

Infra-red Spectra.—The spectra of certain of the compounds mentioned above will be presented and discussed in another series.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, May 1st,* 1953.]

677. *The Thermochemistry of Organo-boron Compounds. Part II.* Tri-n-butylboron, and the Di-n-butylboron Halides.*

By H. A. SKINNER and T. F. S. TEES.

Values are reported for the heats of reaction of liquid tributylboron (*a*) with hydrogen bromide at 56·5° ($\Delta H = -22{\cdot}6 \pm 1$ kcal./mole) and (*b*) with hydrogen iodide at 25° ($\Delta H = -20{\cdot}2 \pm 0{\cdot}7$ kcal./mole). The heats of hydrolysis of the liquid dibutylboron halides in water at 25° were measured as follows: chloride, $\Delta H = -18{\cdot}54 \pm 0{\cdot}2$; bromide, $\Delta H = -21{\cdot}96 \pm 0{\cdot}5$; iodide, $\Delta H = -24{\cdot}94 \pm 0{\cdot}5$ kcal./mole. The latent heats of vaporisation of tributylboron, dibutylboron chloride, and dibutylboron bromide were obtained from vapour-pressure measurements of these substances over a range of temperature.

The assumption that the dissociation energy $D(Bu_2B\text{–}Cl)$ is the same as the mean bond-dissociation energy in boron trichloride, leads to the following values (kcal./mole): $D(Bu_2B\text{–}OH) = 118{\cdot}3$, $D(Bu_2B\text{–}Cl) = 93{\cdot}9$, $D(Bu_2B\text{–}Br) = 74{\cdot}7$, $D(Bu_2B\text{–}I) = 56{\cdot}2$. The differences between these D values are established, although the absolute magnitude of the D values depends on the initial assumption.

THERMOCHEMICAL information on the alkylborons is limited to the single item of the heat of combustion of trimethylboron (Long and Norrish, *Phil. Trans.*, 1949, **241**, *A*, 587). By combining the heat of combustion with the value for the heat of formation of boric oxide (Prosen, Johnson, and Pergiel, Nat. Bur. Stand. Report No. 1552, March, 1952), one may derive the heat of formation of trimethylboron, *viz.*, $\Delta Hf°$ (BMe_3, liq.) = −33·5 kcal./mole, and $\Delta Hf°$ (BMe_3, gas) = −27·8 kcal./mole. Long and Norrish estimate the limits of error in the combustion heat measurements at 0·4%, or ±3 kcal./mole; Prosen *et al.* assign a maximum error of ±0·75 kcal./mole to their value for $\Delta Hf°$ (B_2O_3, cryst.), so that the overall error associated with $\Delta Hf°$ (BMe_3) may be *ca.* ±4 kcal./mole. These data lead to a derived value for the *mean* B–CH_3 bond-dissociation energy in trimethylboron of 74·3 ± 3 kcal./mole (cf. Part I, *loc. cit.*).

In this paper, we report some thermochemical studies on tri-*n*-butylboron and on the di-*n*-butylboron halides: this work is part of a series of studies on boron compounds now being made. The chemistry of tri-*n*-butylboron has been examined in detail by Johnson, Snyder, and van Campen (*J. Amer. Chem. Soc.*, 1938, **60**, 115), who describe a number of the simpler reactions, some of which are stated to take place quantitatively. Such reactions should prove amenable to thermal study, and one of them (tributylboron and hydrogen bromide) is examined here. The reaction

$$BBu_3 + HBr \longrightarrow BBu_2Br + n\text{-}C_4H_{10} \quad . \quad . \quad . \quad . \quad . \quad (1)$$

takes place with moderate speed at 60°, and gives an almost quantitative yield (>99%) of dibutylboron bromide. This reaction (and the similar reaction with hydrogen iodide) was studied thermally in the adiabatic calorimeter described below.

Di-*n*-butylboron chloride may be prepared by the analogous reaction to (1) with hydrogen chloride and we have found that the reaction of tributylboron and hydrogen iodide takes place easily at room temperature to give dibutylboron iodide, a compound not previously described. Each of the dibutylboron halides is hydrolysed readily, and the heats of hydrolysis are now reported.

* Part I, Charnley, Skinner, and Smith, *J.*, 1952, 2288.

Experimental

(a) *Preparation of Compounds.*—Tri-*n*-butylboron was prepared by interaction of the complex of boron trifluoride and ethyl ether with *n*-butylmagnesium bromide, according to Johnson, Snyder, and van Campen (*loc. cit.*). The crude product was purified by fractional distillation in a pure nitrogen atmosphere at low pressure (5—8 mm.).

Di-*n*-butylboron chloride was prepared, as described by Booth and Kraus (*J. Amer. Chem. Soc.*, 1952, **74**, 1415), by interaction of hydrogen chloride with tributylboron at 110°. The bromide was prepared by the analogous reaction at 60°, and the iodide by passing hydrogen iodide through tributylboron at room temperature. The halide derivatives were purified by fractional distillation at low pressures; the chloride and bromide (both of which are more volatile than tributylboron) were thus obtained pure without difficulty; but the iodide, which is of very similar volatility to tributylboron, could not be completely separated from the trialkylboron, and the best samples prepared were not more than 90—95% pure.

Tributylboron and the dibutylboron halides are rapidly oxidised in air, and all manipulation of these compounds was done *in vacuo* or in an atmosphere of pure nitrogen.

(b) *Calorimeters.*—The adiabatic calorimeter was designed and built for us by Dr. T. Charnley. The reactions were carried out in the glass reaction vessel (see figure), the body of which was completely immersed in transformer oil contained in a Dewar vessel of *ca.* 1 l. capacity. The Dewar vessel itself was encased by a metal can, fitted with a flanged metal lid. The whole assembly of the Dewar vessel was immersed in the outer oil-bath. A set of differential thermocouples, working between the contents of the Dewar flask and the outer oil-bath, operated heaters in the latter to maintain a small constant temperature difference between the two; the adiabatic condition was held automatically by a galvanometer–photocell control, similar to that described by Carson, Hartley, and Skinner (*Proc. Roy. Soc.*, 1949, **195**, *A*, 500). The glass reaction vessel was divided by a flat plate into an upper reaction compartment, of *ca.* 190 c.c. capacity, and a lower mercury-filled compartment which gave ballast to the vessel. A capillary inlet, entering the reaction vessel centrally, terminated at the upper end in a cone-tap seal. The reaction vessel was floated on a pool of mercury lying in the bottom of the Dewar vessel, and was held in a central position within the Dewar flask by a bearing in the flange lid. The reaction vessel could be rotated at constant speed (150 r.p.m.) by a drive from an induction motor to the capillary inlet. The motor was supported vertically above the oil tank. The temperature of the calorimetric fluid (light transformer oil) was measured in terms of the resistance of a shielded thermistor element. This was held in a fixed position in the Dewar vessel from a chimney in the flange lid. Two similar chimneys allowed the entrance of the Dewar thermocouples (ten copper–constantan units in series) and of an encased wire-wound heating-coil. This latter was used in the electrical calibration of the calorimeter, and it also served to supply heat to the contents of the Dewar vessel to bring them to the desired starting temperature.

The hydrolysis reactions were carried out in the calorimeter previously described in Part I (*loc. cit.*). The hydrolyses were studied at 25°.

(c) *Units.*—The unit of heat in which all the results are given is the thermochemical calorie (4·1840 abs. joules).

(d) *Vapour Pressures.*—The vapour pressures of pure samples of tributyboron, dibutylboron chloride, and dibutylboron bromide were measured over a range of temperature (20—90°) in an apparatus similar to that described by Burg and Schlesinger (*J. Amer. Chem. Soc.*, 1937, **59**, 780). The results are presented in the vapour-pressure equations given below, from which the latent heats of vaporisation were derived by application of the Clapeyron–Clausius equation:

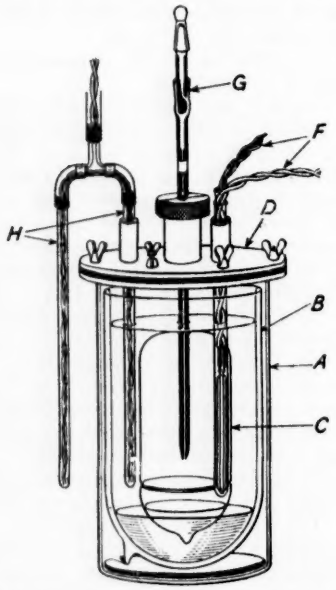
Tributylboron: $\log p = 8{\cdot}797 - 2857/T$; $\lambda_{vap.} = 13{\cdot}07$ ($\pm 0{\cdot}25$) kcal./mole.
Dibutylboron bromide: $\log p = 8{\cdot}682 - 2643/T$; $\lambda_{vap.} = 12{\cdot}09$ ($\pm 0{\cdot}20$) kcal./mole.
Dibutylboron chloride: $\log p = 8{\cdot}592 - 2518/T$; $\lambda_{vap.} = 11{\cdot}52$ ($\pm 0{\cdot}20$) kcal./mole.

Results.—(a) *Reaction of hydrogen bromide with tributylboron.* This reaction was studied at 56·5°, at which temperature complete reaction times of 1—2 hr. were required, and adiabatic calorimetry was adopted to deal with this comparatively slow reaction. The reaction occurs cleanly, yielding butane and dibutylboron bromide. The extent of the reaction was analysed by measuring the volume of butane produced, and by titration of the bromide ion obtained on hydrolysis of the dibutylboron bromide formed.

The experimental procedure was as follows: a sample of tributylboron was distilled from stock *in vacuo*, and condensed in the reaction vessel, which was then fitted in position in the

Dewar vessel, the flanged lid bolted on, and the assembly lowered into the outer oil-bath. The temperature of both bath and Dewar flask contents was raised to *ca.* 56°, and the automatic adiabatic control mechanism then set in action. The reaction vessel was connected to the stirring motor, and the system allowed to reach thermal equilibrium.

The thermistor resistance was measured at regular intervals during an hour or more, before the reaction was started. The stirring motor was then temporarily disconnected,* whilst hydrogen bromide (preheated to the bath-temperature) was allowed to enter and fill the reaction vessel *via* the cone-tap seal of the capillary inlet. (The tributylboron was present, initially, under vacuum; on the cone-tap's being turned, the hydrogen bromide entered to fill the vacuous space.) The reaction vessel then reconnected to the stirring motor, and the measurements of the thermistor resistance were recorded for a further period of *ca.* 120 min.



A, Metal can; B, Dewar vessel; C, glass reaction vessel; D, flanged lid; F, thermistor and heater leads; G, cone-tap seal; H, thermocouples.

The reaction vessel was removed from the calorimeter, and attached to the gas-analysis apparatus. The volume of butane was measured at 20° (corrections to ideal gas and standard conditions were made from the data of Sagi, Webster, and Lacey, *Ind. Eng. Chem.*, 1937, **29**, 118). The dibutylboron bromide (retained in the reaction vessel) was hydrolysed with distilled water, and the hydrobromic acid determined by titration (Volhard's method). In general, agreement within 2% was attained between the analyses based on butane and those based on bromide ion.

The observed heats ($\Delta H_{obs.}$) of the reaction (at 56·5°):

$$BBu_3 \text{ (liq.)} + HBr \text{ (g.)} \longrightarrow BBu_2Br \text{ (liq.)} + BuH \text{ (g.)} \quad . \quad . \quad . \quad (2)$$

are listed in Table 1. Here, the moles of borine are mean values as determined by butane and bromide-ion analyses. The final column of Table 1 gives the values of $(x - a)$, where $x = \Delta Hf°$ (BBu_3, liq.), and $a = \Delta Hf°$ (BBu_2Br, liq.), derived from the thermal equation †:

$$(x - a) = \Delta Hf° \text{ (BuH, g.)} - \Delta Hf° \text{ (HBr, g.)} - \Delta H_{obs.} \quad . \quad . \quad . \quad (3)$$

The values $\Delta Hf°$ (BuH, g.) = −29·81 kcal./mole and $\Delta Hf°$ (HBr, g.) = −8·66 kcal./mole recommended in N.B.S. tables (Circular 500), were used in calculating $(x - a)$. The overall limits of error in $\Delta H_{obs.}$ we would estimate at *ca.* ±1 kcal./mole, arising partly from the possible

* Correction for the stirring-heat loss during this period was made by applying a similar stirring interruption in the electrical calibration experiments.

† In this equation, we have assumed that the observed heat of reaction at 56·5° may be carried over unchanged to the standard temperature of 25°, and that the heats of mixing of liquid dibutylboron bromide with the excess of tributylboron, and of solution of the gaseous butane in the small volume of liquid product in the reaction vessel, are negligible.

error of *ca.* ±2% in the estimation of the moles of borine which reacted, and from an error of similar magnitude in the operation of the calorimeter.

TABLE 1. *Reaction of tributylboron and hydrogen bromide.*

Expt.	BBu_3 (10^{-2} mole)	$-\Delta H_{obs.}$ (kcal.)	$(x - a)$ (kcal.)	Expt.	BBu_3 (10^{-2} mole)	$-\Delta H_{obs.}$ (kcal.)	$(x - a)$ (kcal.)
1	0·7585	22·33	1·18	4	0·7474	23·42	2·27
2	0·7606	22·87	1·72	5	0·7678	22·09	0·94
3	0·7716	22·11	0·96		Mean values	22·56	1·41

(b) *Reaction of hydrogen iodide with tributylboron.* This reaction occurs at moderate speed at room temperature, so we were able to investigate it at the standard temperature (25°). Otherwise, the procedure was similar to that used in the analogous reaction with hydrogen bromide. The extent of reaction was measured by the volume of butane produced, and by titration of hydrolysable iodine in the product, dibutylboron iodide. Good agreement (generally within 1%) was obtained between these two measures.

A selection from the results is presented in Table 2. Observed reaction heats are listed under $\Delta H_{obs.}$, and the final column gives values of $(x - b)$, where $x = \Delta Hf°$ (BBu_3, liq.), $b = \Delta Hf°$ (BBu_2I, liq.), derived from the thermal equation

$$(x - b) = \Delta Hf° (BuH, g.) - \Delta Hf° (HI, g.) - \Delta H_{obs.} \quad . \quad . \quad . \quad . \quad (4)$$

The values recommended in the N.B.S. tables (Circular 500) were accepted, *viz.*, $\Delta Hf°$ (BuH, g.) = −29·81, $\Delta Hf°$ (HI, g.) = 6·20 kcal./mole.

TABLE 2. *Reaction of tributylboron and hydrogen iodide.*

Expt.	BBu_3 (10^{-2} mole)	$-\Delta H_{obs.}$ (kcal.)	$(x - b)$ (kcal.)	Expt.	BBu_3 (10^{-2} mole)	$-\Delta H_{obs.}$ (kcal.)	$(x - b)$ (kcal.)
1	0·8542	20·24	−15·77	4	0·8129	20·04	−15·97
2	0·8620	20·00	−16·01	5	0·7915	20·35	−15·66
3	0·7900	20·15	−15·86		Mean values	20·16	−15·85

TABLE 3. *Heats of hydrolysis of dibutylboron halides.*

Halide (10^{-2} mole)	n	$-\Delta H_{obs.}$ (kcal.)	$y - \Delta Hf°$ (Bu_2BX) (kcal.)	Halide (10^{-2} mole)	n	$-\Delta H_{obs.}$ (kcal.)	$y - \Delta Hf°$ (Bu_2BX) (kcal.)
			Dibutylboron chloride.				
0·6547	6400	18·45	−46·79	0·5620	7400	18·64	−46·98
0·8680	4800	18·56	−46·91	1·635	2500	18·48	−46·85
0·8350	5000	18·57	−46·92	Mean values:		18·54	−46·89 (± 0·2)
			Dibutylboron bromide.				
0·4563	9100	22·00	−61·46	0·5415	7700	21·41	−60·85
0·5502	7570	22·00	−61·46	0·6950	6050	21·94	−61·40
0·5931	7050	22·47	−61·93	Mean values:		21·96	−61·42 (±0·5)
			Dibutylboron iodide.				
0·6097	6850	24·81	−79·79	0·8805	4730	24·99	−79·98
0·5693	7300	25·54	−80·52	0·5183	8000	24·58	−79·56
0·7508	5550	24·73	−79·72	Mean values:		24·94	−79·93 (±0·5)
0·5970	7000	25·01	−79·99				

The overall error in $\Delta H_{obs.}$ is estimated at *ca.* ±¾ kcal./mole.

(c) *Hydrolysis of the dibutylboron halides.* The dibutylboron halides are hydrolysed rapidly at room temperature, to form the corresponding halogen hydracids and dibutylboronic acid, $Bu_2B{\cdot}OH$, which is a sparingly soluble oily liquid absorbing oxygen from the air with evolution of heat. To avoid the spurious thermal effects that might ensue from this oxidation process, all the hydrolysis experiments were conducted under an atmosphere of pure nitrogen.

The measured heats of hydrolysis ($\Delta H_{obs.}$) given in Table 3 refer to the general equation :

$$Bu_2BX(liq.) + (n + 1)H_2O(liq.) \longrightarrow Bu_2B{\cdot}OH(liq.) + HX,nH_2O(soln.) \quad . \quad . \quad (5)$$

This equation leads to the thermochemical relation

$$\Delta Hf° (Bu_2B{\cdot}OH, liq.) - \Delta Hf° (Bu_2BX, liq.) = \Delta H_{obs.} + \Delta Hf° (H_2O, liq.) - \Delta Hf° (HX,nH_2O) \quad . \quad (6)$$

The value of $\Delta Hf°$ ($Bu_2B{\cdot}OH$, liq.) is represented in Table 3 by the symbol y, and is not known independently at present. The values of $\Delta Hf°$ (H_2O, liq.) and $\Delta Hf°$ (HX,nH_2O) were taken from the N.B.S. tables (Circular 500).

The experiments were conducted by breaking thin glass ampoules containing known weights of dibutylboron halide under the surface of 750 g. of distilled water, contained in the Dewar-vessel calorimeter. The temperature changes were followed in terms of the resistance change of a shielded thermistor element immersed in the reaction vessel. At the end of each experiment, aliquot samples of the solution in the Dewar vessel were analysed for their halogen content (Volhard's method), as a check on purity of the dibutylboron halide used. The samples of dibutylboron chloride and bromide were found to be not less than 99% pure, but the iodide was only 90—95% pure (see p. 3379). The thermal results given on dibutylboron iodide in Table 3 are based on the purity as determined by halogen content.

Discussion

The results of the previous section may be summarised in the five equations (all in terms of kcal./mole), *viz.*, (i) $x - a = 1{\cdot}41 \pm 1$, (ii) $x - b = -15{\cdot}85 \pm 0{\cdot}75$, (iii) $y - a = -61{\cdot}42 \pm 0{\cdot}5$, (iv) $y - b = -79{\cdot}93 \pm 0{\cdot}5$, and (v) $y - c = -46{\cdot}89 \pm 0{\cdot}2$, where $c = \Delta Hf^\circ$ (BBu_2Cl, liq.), and x, y, a, and b have already been defined. By combining equations (i) and (ii), one obtains $(a - b) = -17{\cdot}26 \pm 1{\cdot}75$, compared with $(a - b) = -18{\cdot}51 \pm 1{\cdot}0$ from equations (iii) and (iv). The equations are thus not entirely consistent with each other, although the inconsistencies appear to lie well within the combined error limits attached to the individual measurements.

It is convenient to express the quantities y, a, b, and c in terms of the single unknown, x. The following mean values are obtained:

$$y = \Delta Hf^\circ\ (BBu_2{\cdot}OH,\ liq.) = x - 63{\cdot}45\ (\pm 1{\cdot}4)\ kcal./mole \quad . \quad . \quad . \quad (7)$$

$$c = \Delta Hf^\circ\ (BBu_2Cl,\ liq.) = x - 16{\cdot}56\ (\pm 1{\cdot}6)\ kcal./mole \quad . \quad . \quad . \quad (8)$$

$$a = \Delta Hf^\circ\ (BBu_2Br,\ liq.) = x - 1{\cdot}72\ (\pm 1{\cdot}5)\ kcal./mole \quad . \quad . \quad . \quad (9)$$

$$b = \Delta Hf^\circ\ (BBu_2I,\ liq.) = x + 16{\cdot}16\ (\pm 1{\cdot}4)\ kcal./mole \quad . \quad . \quad (10)$$

In these equations, x is the heat of formation of *liquid* tributylboron; for the further discussion we shall require the set of equations (11)—(14), in which the ΔHf° terms relate to the *gaseous* states of the molecules concerned, *viz.*:

$$y' = \Delta Hf^\circ\ (BBu_2{\cdot}OH,\ g.) = x' - 61{\cdot}5\ (\pm 3)\ kcal./mole \quad . \quad . \quad . \quad (11)$$

$$c' = \Delta Hf^\circ\ (BBu_2Cl,\ g.) = x' - 18{\cdot}11\ (\pm 2)\ kcal./mole \quad . \quad . \quad . \quad (12)$$

$$a' = \Delta Hf^\circ\ (BBu_2Br,\ g.) = x' - 2{\cdot}70\ (\pm 2)\ kcal./mole \quad . \quad . \quad . \quad (13)$$

$$b' = \Delta Hf^\circ\ (BBu_2I,\ g.) = x' + 16{\cdot}1\ (\pm 2{\cdot}2)\ kcal./mole \quad . \quad . \quad . \quad (14)$$

Eqns. (11)—(14) make use of the heats of vaporisation given on p. 3379, and of two *assumed* values,* $\lambda_{vap.}$ (BBu_2I) $= 13 \pm 0{\cdot}5$, and $\lambda_{vap.}$ ($BBu_2{\cdot}OH$) $= 15 \pm 2$ kcal./mole.

Although the value x' has not yet been determined, it is nevertheless possible to examine a number of bond-energy inter-relations in these molecules, starting from the equations (11)—(14). Consider the (gaseous) dissociation process $Bu_2BX \longrightarrow Bu_2B + X$, and let the heat of disruption (the bond-dissociation energy) be represented by $D(Bu_2B{-}X)$; correspondingly, for the process $Bu_2BY \longrightarrow Bu_2B + Y$, the bond-dissociation energy is represented by $D(Bu_2B{-}Y)$. Then we may write, quite generally, the thermal equation:

$$\Delta D\begin{bmatrix} X \\ Y \end{bmatrix} = D(Bu_2B{-}X) - D(Bu_2B{-}Y) = \Delta Hf^\circ\ (X) - \Delta Hf^\circ\ (Y) + \Delta Hf^\circ\ (BBu_2Y) - \Delta Hf^\circ\ (BBu_2X) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

Accepting the values (recommended in the N.B.S. tables) ΔHf° (OH, g.) $= 10{\cdot}0$, ΔHf° (Cl, g.) $= 29{\cdot}0$, ΔHf° (Br, g.) $= 26{\cdot}7$, and ΔHf° (I, g.) $= 25{\cdot}5$ kcal./mole, together with the eqns. (11)—(14), and applying eqn. (15), we obtain:

$$\Delta D\begin{bmatrix} OH \\ Cl \end{bmatrix} = 24{\cdot}4\ (\pm 5)\ kcal./mole,\ \Delta D\begin{bmatrix} Cl \\ Br \end{bmatrix} = 17{\cdot}7\ (\pm 4),\ and\ \Delta D\begin{bmatrix} Br \\ I \end{bmatrix} = 20{\cdot}0\ (\pm 4).$$

* The similarity in volatility of BBu_2I and BBu_3 suggests that the values of $\lambda_{vap.}$ of these compounds are of the same magnitude. The $\lambda_{vap.}$ of alcohols, relative to alkyl iodides, are generally larger by 2—3 kcal./mole, and a similar difference is assumed between the $\lambda_{vap.}$ of $BBu_2{\cdot}OH$ and BBu_2I.

These ΔD relations represent the limiting point to which we can go in a strict manner at present. To proceed further requires the measure of at least one of the D values involved, or alternatively, we need to introduce at least one assumption.

The assumption commonly made in problems of this type is also the simplest—*i.e.*, the assumption of constant bond-energy terms, transferable from one molecule to another. In the present case, *e.g.*, we might assume that $D(Bu_2B–Cl)$ is the same as the mean bond-dissociation energy, $\bar{D}$(B–Cl), in boron trichloride. The heat of formation of boron trichloride has been determined recently by Skinner and Smith (*Trans. Faraday Soc.*, 1953, **49**, 601) and by Johnson, Miller, and Prosen (N.B.S. Report No. 2257, Jan., 1953), from which the value $\bar{D}$(B–Cl) = 93·9 kcal./mole may be derived [$\Delta Hf°$ (BCl_3, g.) = −97·5; $\Delta Hf°$ (B, g.) = 97·2 kcal./mole]. The identification of D(B–Cl) with $D(Bu_2B–Cl)$ then leads to the additional values: $D(Bu_2B–OH)$ = 118·3 $D(Bu_2B–Br)$ = 76·2, and $D(Bu_2B–I)$ = 56·2 kcal./mole. It is encouraging to note that the value obtained for $D(Bu_2B–Br)$ is close to the value, $\bar{D}$(B–Br) = 74·7 kcal./mole, determined from the heat of formation of boron tribromide (Part I, *loc. cit.*)—so that we may accordingly predict the unknown D(B–I) in boron tri-iodide at 56 ± 5 kcal./mole with some measure of confidence. The value obtained for $D(Bu_2B–OH)$ is appreciably larger than the run of values $\bar{D}$(B–OR) in the alkyl borates, $B(OR)_3$ (Charnley, Mortimer, and Skinner, *J.*, 1953, 1181), but this is a not uncommon feature that emerges from a comparison of dissociation energies of the type M–OH and M–OR—*e.g.*, D(H–OH) = 119 kcal./mole, whereas D(H–OMe) = 99 kcal./mole.

The assumption of constant transferable bond-energy terms may be alternatively expressed in the statement that redistribution reactions involve no overall change in enthalpy.* Applied to the present case, this assumption would allow us to write: $2BBu_3(g.) + BCl_3(g.) \longrightarrow 3BBu_2Cl(g.)$, $\Delta H = 0$, from which it would follow that $x' = \Delta Hf°$ (BBu_3, g.) = −43·2 (±7) kcal./mole. This estimate leads to the value $\bar{D}$(B–Bu) = 66·3 (±3) kcal./mole [$\Delta Hf°$ (Bu, g.) = 19·5 (±1) kcal./mole, from Mortimer, Pritchard, and Skinner, *Trans. Faraday Soc.*, 1952, **48**, 220, and Stevenson, *Discuss. Faraday Soc.*, 1951, **10**, 113].

However, several redistribution reactions are known which do not comply with the thermoneutrality condition as required by the simple postulate of constant bond-energy terms. The reactions, for example, of the type $HgR_2 + HgX_2 \longrightarrow 2HgRX$ (Hartley, Pritchard, and Skinner, *Trans. Faraday Soc.*, 1950, **46**, 1019; and later papers in this series) are usually exothermic, and we suspect that the reaction discussed above may be similar in this respect. We reserve further comment pending an independent determination of the heat of formation of tributylboron.

Added in Proof.—Our attention has recently been drawn to a new determination of the heat of sublimation of boron by Searcy and Myers, who obtained $\Delta Hf°$ (B,g.) = 140·9 ± 2·0 kcal./mole. This value differs appreciably from the figure recommended in the N.B.S. tables (97·2 kcal./mole) which is used in this paper. If the new value is accepted, *all* D and $\bar{D}$ values of boron bonds given in the text are *increased* in magnitude by 14·6 kcal./mole.

The authors thank Dr. T. Charnley for his assistance in the construction of the adiabatic calorimeter used in this work.

Chemistry Dept., University of Manchester. [*Received, June 5th*, 1953.]

* A redistribution reaction is one in which bonds may change in relative position, but not in total number or formal character.

678. *The Kinetics of the Reduction by Titanous Chloride of Nitrobenzene and its Substitution Products.*

By S. A. Newton, jun., F. J. Stubbs, and Sir Cyril Hinshelwood.

The reduction of nitrobenzene by titanous chloride in aqueous alcohol is of the first order with respect to each of these reactants and, over a certain range, inversely proportional (approximately) to the square of the hydrogen-ion concentration. The active species are thought to be $Ph{\cdot}NO_2H^+$ and a hydrolysed form of titanous ion. In the sequence $Ph{\cdot}NO_2$(1) $\longrightarrow$ $Ph{\cdot}NO$(2) $\longrightarrow$ $Ph{\cdot}NH{\cdot}OH$(3) $\longrightarrow$ $Ph{\cdot}NH_2$, (2) and (3) are reduced many times more rapidly than (1), but condensation leads to a very rapid formation of azoxybenzene which, although it yields aniline quantitatively, is reduced much more slowly. The diversion of a considerable part of the reaction by way of the azoxy-compound leads to a fall in bimolecular constants, but the rate of titanous ion consumption at each stage can be quantitatively accounted for in terms of the reaction scheme given.

Substituents in the benzene nucleus have the effect expected from their electronic character if the rate-determining step is a transfer of electrons from titanous complex to nitro-compound.

In the majority of examples the joint effect of two substituents on the free energy of activation is calculable additively from their individual actions. Deviations are attributable to a saturation effect with two powerfully acting groups, or to chelate interactions.

The entropy of activation is not constant for the whole series of reactions but tends to rise with the activation energy.

The present study will deal first with the kinetics of the reduction of nitrobenzene by titanous chloride in aqueous alcohol, and secondly with the influence of other substituents in the benzene nucleus on the reaction.

Course of the Reaction.—According to the scheme put forward by Haber (*Z. phys. Chem.*, 1900, **32**, 193) the reduction of nitrobenzene goes through the stages

$$Ph{\cdot}NO_2 \longrightarrow Ph{\cdot}NO \longrightarrow Ph{\cdot}NH{\cdot}OH \longrightarrow Ph{\cdot}NH_2$$

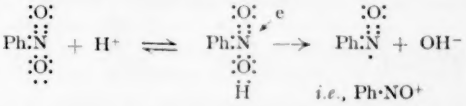
and in appropriate conditions $Ph{\cdot}NO$ and $Ph{\cdot}NH{\cdot}OH$ interact to give $Ph{\cdot}NO{:}NPh$. The azoxybenzene is itself reduced to aniline by titanous chloride but more slowly than nitrobenzene.

Under the conditions employed (concentration of Ti^{3+} 0·006—0·024N, $Ph{\cdot}NO_2$ 0·001—0·004M, hydrion 0·24—1·28N) the reduction of nitrosobenzene or of phenylhydroxylamine is very many times more rapid than that of nitrobenzene, and the interaction of these two compounds to give azoxybenzene is also extremely fast. On the other hand, the rate of reduction of azoxybenzene is only about one seventh as fast as that of nitrobenzene at the same molar concentration.

The rate of consumption of titanous chloride is proportional initially to the concentration of the nitrobenzene and to that of the titanous salt. The consumption of titanous salt does not yield a steady bimolecular constant but one which falls markedly with time. The total reducing agent used up is, however, that theoretically required for the formation of aniline. The facts are accounted for if small concentrations of nitrosobenzene and of phenylhydroxylamine are built up and if interaction of the latter with the former competes with its reduction to aniline, the azoxy-compound formed being itself reduced to aniline but much more slowly.

Reacting Species.—The rate of reaction over the experimental range proves to be proportional to [titanous salt][nitrobenzene]/$[H^+]^2$. The predominant species from nitrobenzene may be assumed to be $Ph{\cdot}NO_2$ itself, but the reactant might be $Ph{\cdot}NO_2H^+$. If it were, the concentration, X, of the active species from the titanous salt would be inversely proportional to the cube of $[H^+]$. If the reactant is $Ph{\cdot}NO_2$ then X is proportional to $1/[H^+]^2$.

The rate-determining step in the reduction is the conversion of nitrobenzene into nitrosobenzene, which demands the transfer of two electrons. This reaction itself is almost certain to occur in two steps, only one of which is rate-determining. The simplest process, in view of the known basic character of nitrobenzene, involves the primary addition of a hydrion, according to the following scheme :

(1) 

(2) $Ph{\cdot}NO^+ + e \longrightarrow Ph{\cdot}NO$ (rapid)

In this the rate-determining step would be the communication of the electron from the titanous species to the $Ph{\cdot}NO_2H^+$.

On this basis the nitrobenzene is positively charged, and will react best with a titanous species not bearing a positive charge itself. If the equilibrium $Ti^{3+} + 3OH^- \rightleftharpoons Ti(OH)_3$ is assumed, the concentration of the hydroxide, or of the TiO(OH) derived from it, would be inversely proportional to the cube of the hydrion concentration. The TiO(OH) would lose an electron in reduction to give $TiO(OH)^+$, the titanic form. But it may not be permissible to assume, as is here tacitly done, that Ti^{3+} is the predominant species in solution, so that the conclusion must be regarded with reserve. In any case simple variants of the above scheme are conceivable. What is clear, however, seems to be that the major reducing species is a hydrolysed form of the titanous salt, present in acid solution only as a minor constituent.

Experimental Method.—The solvent consisted of a mixture of equal volumes of ethyl alcohol and water (42·5% of alcohol by weight). The nitro-compound was dissolved in absolute alcohol and the titanous salt in aqueous hydrochloric acid, the concentrations being such that mixing of the appropriate amounts led to the required initial concentrations of reactants (corrections for the contraction on mixture being made). The reaction was followed by determination of residual titanous ion. Samples were pipetted into standard ferric alum, the excess of which was titrated with titanous chloride solution, stored in an atmosphere of hydrogen. Reaction vessels and titration flasks were kept filled with carbon dioxide from a cylinder, and solutions were de-aerated before use. Pipettes were flushed out with carbon dioxide before use.

The hydrion concentration of the titanous solutions was determined electrometrically, acid–alkali titration indicators being useless.

Influence of Initial Concentrations.—Proportionality of initial rate to titanous salt concentration is shown in Table 1, to nitrobenzene concentration in Table 2, and (approximately) to $1/[H^+]^2$ in Table 3. The rate plotted against the reciprocal of $[acid]^2$ gives a straight line, but with a small intercept on the rate axis which is allowed for in the third column of Table 3.

TABLE 1.

$[Ph{\cdot}NO_2] = 0{\cdot}004$M, $[H^+] = 0{\cdot}48$N.

$[TiCl_3]$, N	0·024	0·018	0·012	0·006
Rate	6·4	4·6	3·0	1·4
$10^{-2} \times$ Rate/$[TiCl_3]$	2·67	2·56	2·50	2·33

Note. Rates are in arbitrary units (*i.e.*, titres of test portions). For absolute values see Tables of k values.

TABLE 2.

$[TiCl_3] = 0{\cdot}024$N, $[H^+] = 0{\cdot}48$N.

$[Ph{\cdot}NO_2]$, M	0·004	0·003	0·002	0·001
Rate	6·4	4·8	3·2	1·5
$10^{-3} \times$ Rate/$[Ph{\cdot}NO_2]$	1·60	1·60	1·60	1·50

Additions of titanic salts or of aniline had no effect on the rate, so that the fall in the bimolecular constant is not due to retardation by products. Thus: Ti^{3+} 0·012N, $Ph{\cdot}NO_2$ 0·002M, rate = 1·50 units; with addition of 0·012N-Ti^{4+}, rate = 1·48; with addition of

TABLE 3.

$[TiCl_3]$ = 0·012M. $[Ph{\cdot}NO_2]$ = 0·002M.

Acid, N	0·24	0·337	0·48	1·28
Rate	5·2	2·8	1·5	0·45
10 (Rate − 0·27) [Acid]^2	2·84	2·87	2·82	2·95

0·002M-$Ph{\cdot}NH_2$, rate = 1·55 units. Addition of large amounts of sodium chloride showed that the effect of changed hydrogen chloride concentration was mainly due to variation of hydrion rather than of chlorine-ion concentration, but revealed also a rather complex

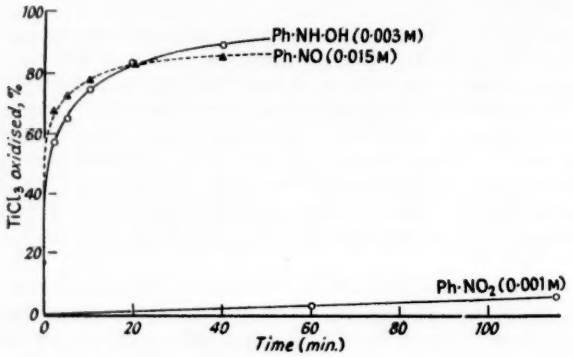


FIG. 1.
$TiCl_3$ 0·006N.
Acid 1·0N.
At 18°.

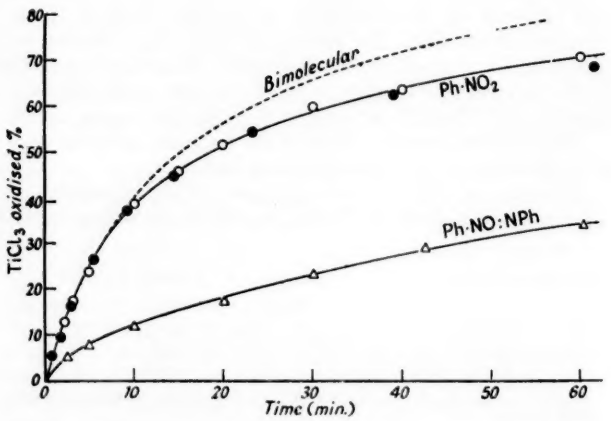


FIG. 2.
25°; $Ph{\cdot}NO_2$ 0·004M, Ph·NO:NPh 0·004M, Ti^{3+} 0·024N, *acid* 0·48N.

general salt effect which was not investigated further. The glass surface of containing vessels was without influence.

Second-order Velocity Constants.—These are not steady but drop as the reaction proceeds. The drop in the velocity constants can be inferred immediately from Fig. 2, and is also shown in Table 4.

TABLE 4.

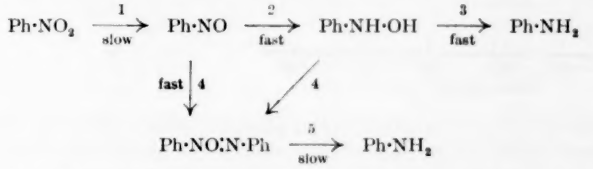
Time (min.)	1·75	4·05	7·00	11·4	20·0	34·0
$TiCl_3$ oxidised, %	10	20	30	40	50	60
k (bimol.)	2·65	2·57	2·55	2·40	2·08	1·84

End-points.—With sufficient titanous chloride for complete reduction the reaction reaches the theoretical end-point.

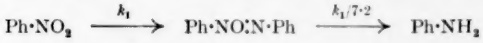
Reaction Rates of Intermediate Reduction Steps.—Nitrosobenzene and phenylhydroxylamine are reduced very many times more rapidly than nitrobenzene, as shown in Fig. 1. (Titanous salt concentration 0·006N, and hydrion 1·0N in each case. Nitrobenzene 0·001M nitrosobenzene 0·0015M, phenylhydroxylamine 0·003M.) Azoxybenzene is reduced much more slowly than nitrobenzene (Fig. 2).

The rapid interaction of nitrosobenzene and phenylhydroxylamine under the reaction conditions was shown by the following experiment. Equivalent quantities (0·004M) were mixed and allowed to stand for a few minutes in a solution of the same pH as the normal reaction mixture. Titanous salt equivalent to the total was then added and the reaction followed in the normal way. A considerable part of the rapidly reducible material was found to have disappeared during the interaction of the two compounds and to have been replaced by a compound which was much more slowly reduced. This was presumably the azoxy-compound.

Form of Reaction–Time Curves.—Nitrosobenzene and phenylhydroxylamine are both reduced with very great speed. Their interaction is also very fast so that it is difficult to predict what proportion of the reaction will take place by way of the azoxy-compound in the system



Certain empirical trials were therefore made. Values were assumed for the appropriate velocity constants and the reaction–time curves were calculated by arithmetical computation for successive small time intervals (the integration of the differential equation being intractable). The results appeared to show that practically all the reduction followed the course 1, 2, 4, 5. The evidence is given in Fig. 2. Here the rate of reduction of azoxybenzene is shown to be 3·6 times as slow, in terms of titanous ion consumed, as that of an equimolar solution of nitrobenzene. If 1 g.-mol. of nitrobenzene gives azoxybenzene it uses up only one half as much of the reducing agent as 1 g.-mol. of the azoxy-compound giving aniline. Thus in a test of the assumption that azoxybenzene is an intermediate stage for practically all the nitrobenzene it must be assumed that k for process 1 is $2 \times 3{\cdot}6 = 7{\cdot}2$ times as great as k for process 5. The assumed reaction scheme now simplifies to



k_1 is chosen to give the correct initial slope for the reaction-time curve of nitrobenzene. Computation then gives the points shown by full circles in Fig. 2, the open circles showing the experimental values. The dotted line shows the bimolecular curve. The assumption that azoxybenzene is a major intermediate appears to be justified. The result is a little surprising since although nitrosobenzene and phenylhydroxylamine interact rapidly, the direct reduction of the latter to aniline is also very rapid. What is possible, however, is that the labile odd-electron intermediate which is presumably formed transitorily between nitrosobenzene and phenylhydroxylamine may interact with nitrobenzene even more readily than these compounds react with one another, and give a binuclear substance easily reducible to the azoxy-compound. This matter seems worthy of further investigation.

For the present purpose, however, the important question is to establish the correct basis for the comparison of the various substituted compounds. According to the ratio in which the routes 1, 2, 3 and 1, 2, 4, 5 are followed as the result of the first rate-determining step, the titanous equivalent of the nitro-compound will vary, and this ratio might be different for the different derivatives studied.

Reaction–time curves for 15 compounds varying widely in reactivity were therefore

plotted with the time-scales adjusted to give coincidence at one standard value of the ordinate. As shown in Figs. 3 and 4, all the curves then become nearly superposable. From this may be inferred that the ratio does not vary appreciably from one compound to another. [This conclusion is consistent with the result of Brandt and Mahr (*J. pr. Chem.*, 1931, **131**, 118; 1935, **142**, 161), who found the influence of substituents on the

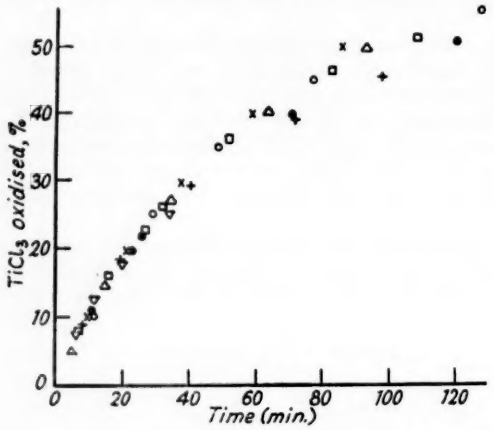


FIG. 3.

Nitrobenzene (30°) × 1·0, o-*nitrophenol* (16°) × 4·3, m-*nitrophenol* (30°) × 0·98, p-*nitrophenol* (25°) × 0·129, o-*nitrotoluene* (35°) × 0·217, m-*nitrotoluene* (25°) × 0·44, p-*nitrotoluene* (35°) × 0·827.

rate of interaction of nitroso-compounds and phenylhydroxylamines to be similar to that found in the present work on the rate of reduction of the nitro-compound.]

The initial rate of reduction expressed in terms of titanous ion consumption can therefore validly be used for comparison of the various nitro-compounds, independently of the (provisional) conclusion that the rate-determining step corresponds stoicheiometrically to the change nitro-compound ⟶ azoxy-compound.

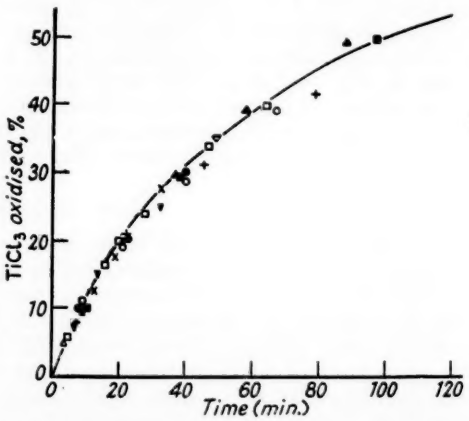


FIG. 4.

o-*Chloronitrobenzene* (20°) × 0·249, p-*chloronitrobenzene* (20°) × 0·933, m-*chloronitrobenzene* (15°) × 0·95, o-*nitroaniline* (25°) × 0·457, m-*nitroaniline* (5°) × 0·385, p-*nitroaniline* (25°) × 1·10, m-*dinitrobenzene* (15°) × 4·4, p-*dinitrobenzene* (15°) × 9·8.

Activation Energies.—These were calculated either directly from the initial rates at a series of temperatures (usually four) or indirectly as follows. Times required for given percentages of reaction at different temperatures were read off from curves and their logarithms were plotted against $1/T$. They gave good linear plots and the values of E were calculated by the method of least squares. A series of activation energies showing a small systematic trend were thus obtained and extrapolation to zero reaction then gave the value corresponding to the initial rate (cf. Table 5). Where both were used the two procedures yielded concordant results.

TABLE 5. *Typical variations of* E *with % of reaction.*

Nitrobenzene		*m*-Nitrophenol		*p*-Chloronitrobenzene		*o*-Nitroaniline	
Reaction, %	*E*	Reaction, %	*E*	Reaction, %	*E*	Reaction, %	*E*
10	18,100	10	16,600	10	18,600	10	17,300
20	18,700	20	18,500	20	19,700	20	17,700
30	19,800	30	19,500	30	20,500	30	18,700
40	21,200	40	19,800	40	20,800	Extrapolated	17,000
50	23,400	50	19,900	Extrapolated	17,300		
Extrapolated	17,500	Extrapolated	17,000				

TABLE 6. *Reduction of substituted nitrobenzenes by titanous chloride.*

Substituent	$k_{20°}$, l g.-mol.$^{-1}$ sec.$^{-1}$	(ΔF^*) (cal.)	Change in (ΔF^*) due to substituent (cal.)	Measured *E*, cal./g.-mol.
(H)	$6{\cdot}78 \times 10^{-2}$	1567	—	17,700
o-OH	1·119	−103	−1670	16,500
m-OH	$6{\cdot}93 \times 10^{-2}$	1554	− 13	17,000
p-OH	$1{\cdot}58 \times 10^{-2}$	2415	+ 848	19,500
o-CH_3	$7{\cdot}43 \times 10^{-3}$	2854	+1287	25,000
m-CH_3	$8{\cdot}4 \times 10^{-2}$	1443	− 124	17,500
p-CH_3	$3{\cdot}87 \times 10^{-2}$	1893	+ 326	20,000
o-Cl	$7{\cdot}43 \times 10^{-2}$	1514	− 53	18,500
m-Cl	$5{\cdot}08 \times 10^{-1}$	536	−1031	16,500
p-Cl	$2{\cdot}42 \times 10^{-1}$	826	− 741	17,300
o-NH_2	$1{\cdot}00 \times 10^{-1}$	1341	− 226	17,000
m-NH_2	$3{\cdot}72 \times 10^{-1}$	577	− 990	16,900
p-NH_2	$1{\cdot}58 \times 10^{-1}$	1074	− 493	16,500
o-NO_2	$5{\cdot}97 \times 10^{-1}$	300	−1267	17,600
m-NO_2	$7{\cdot}75 \times 10^{-1}$	149	−1418	18,200
p-NO_2	1·171	−312	−1879	15,500
o-OCH_3	$1{\cdot}1 \times 10^{-2}$	2622	+1055	21,600
m-OCH_3	$7{\cdot}81 \times 10^{-2}$	1482	− 85	17,800
p-OCH_3	$1{\cdot}4 \times 10^{-2}$	2483	+ 916	20,600
o-CO_2H	$1{\cdot}58 \times 10^{-1}$	1074	− 493	17,200
m-CO_2H	$2{\cdot}33 \times 10^{-1}$	849	− 718	16,200
p-CO_2H	1·081	−46	−1613	17,100

TABLE 7. *Reduction of substituted nitrobenzenes by titanous chloride.*

Substituents		$k_{20°}$	(ΔF^*), cal.: By experiment	(ΔF^*), cal.: Predicted	Change in (ΔF^*) due to substituent: By experiment	Change in (ΔF^*) due to substituent: Predicted
o-CH_3	*m*-NH_2	$6{\cdot}15 \times 10^{-2}$	1624	1864	+ 57	+ 297
m-CH_3	*o*-NH_2	$1{\cdot}75 \times 10^{-1}$	1015	1217	− 552	− 350
p-CH_3	*m*-NH_2	$2{\cdot}91 \times 10^{-1}$	719	903	− 848	− 664
m-CH_3	*p*-NH_2	$2{\cdot}24 \times 10^{-1}$	872	950	− 695	− 617
o-CH_3	*m*-CH_3	$1{\cdot}0 \times 10^{-2}$	2682	2730	+1115	+1163
m-CH_3	*p*-CH_3	$4{\cdot}83 \times 10^{-2}$	1765	1769	+ 198	+ 202
o-CH_3	*p*-CH_3	$6{\cdot}0 \times 10^{-3}$	2979	3170	+1412	+1603
o-CH_3	*o*-CH_3	$1{\cdot}83 \times 10^{-3}$	3671	4141	+2104	+2574
m-Cl	*p*-Cl	$6{\cdot}65 \times 10^{-1}$	239	795	−1328	−1772
o-Cl	*m*-Cl	$3{\cdot}32 \times 10^{-1}$	644	483	− 923	−1084
o-Cl	*m*-NH_2	$2{\cdot}66 \times 10^{-1}$	771	524	− 796	−1043
m-NO_2	*m*-NO_2	1·33	−166	−1269	−1733	−2836
o-NH_2	*m*-OCH_3	$1{\cdot}43 \times 10^{-1}$	1133	1256	− 434	− 311
p-NH_2	*m*-OCH_3	$1{\cdot}56 \times 10^{-1}$	1082	1989	− 485	− 578
m-NH_2	*p*-OCH_3	$6{\cdot}3 \times 10^{-2}$	1610	1493	+ 43	− 74
o-OH	*m*-CO_2H	1·83	−352	− 821	−1919	−2388
p-OH	*m*-CO_2H	$8{\cdot}3 \times 10^{-1}$	108	1697	−1459	+ 130
m-CO_2H	*p*-CO_2H	1·43	−208	− 764	−1775	−2331
m-CO_2H	*o*-CO_2H	$6{\cdot}82 \times 10^{-1}$	223	356	−1344	−1211
m-Cl	*m*-Cl *p*-OH	$1{\cdot}46 \times 10^{-1}$	1121	353	− 446	−1214
m-Cl	*m*-Cl *p*-NH_2	$2{\cdot}83 \times 10^{-2}$	2076	− 988	+ 509	−2555
m-NO_2	*m*-CO_2H	$9{\cdot}3 \times 10^{-1}$	42	− 569	−1525	−2136

Influence of Substituents in the Benzene Ring on the Reduction of the Nitro-group.—All the compounds listed in Table 6 were examined in the way described for nitrobenzene, and for those in Table 7 rate determinations were made at least at a standard temperature.

E (*i.e.*, ΔH^*) is the activation energy derived from the Arrhenius equation and ΔF^*, the so-called free energy of activation, derived from the formula $\Delta F^* = -\boldsymbol{R}T \ln k$, expressing the conventional thermodynamic analogy $k = e^{\Delta S^*/\boldsymbol{R}} e^{-\Delta H^*/\boldsymbol{R}T}$, so that $\Delta F^* = \Delta H^* - T\Delta S^*$. For polynitro-compounds the observed rates are for purposes of comparison divided by the number of nitro-groups.

Discussion.—(a) *Energy–entropy relations.* Fig. 5 shows log k (for 20°) plotted against E. If the entropy of activation is constant, the activation energy plotted against log k gives a straight line of slope $-2{\cdot}303\boldsymbol{R}T$. Fig. 5 shows that in the region of lower activation energies there is some tendency for this relation to be satisfied, although there is a quite considerable and apparently random scatter of the points about the mean line. As the activation energy rises, however, the drop in log k is less than the linear relation predicts, the sharp upward course of the curve corresponding to a definite and systematic increase in the entropy with the energy of activation.

In comparable series of reactions of substituted benzene derivatives a constant entropy of activation has several times been found—for example, in benzoylation of amines, and in alkaline hydrolysis of benzoic esters. A ln k–E relation somewhat similar to that shown

FIG. 5.

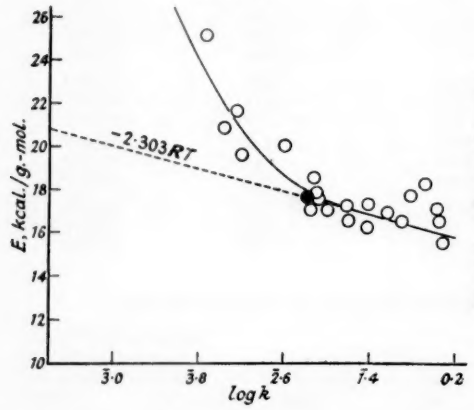
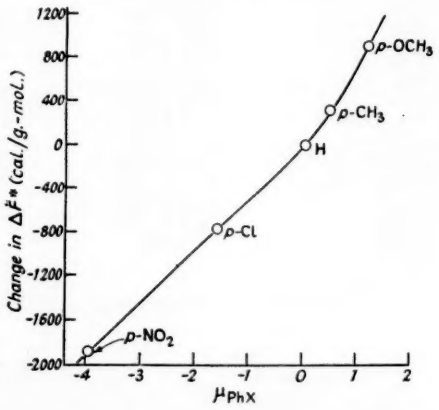


FIG. 6.



in Fig. 5 was found for the benzoylation reaction, and also for the combination of pyridine with methyl iodide, when the variable parameter was not the substituent but the solvent (Pickles and Hinshelwood, *J.*, 1936, 1353).

In view of the non-constancy of the entropy of activation in the present example, the free energy of activation was thought to be a more suitable quantity for the measure of substituent effects, and in particular for the testing of additive relations among them. It has, moreover, the advantage of being more accurately measurable, which is of importance in the present case where the values of E are subject to some experimental uncertainty. If, however, the logarithm of the non-exponential factor is a linear function of E, as it not infrequently is, then of course additivity in the free energy would imply a similar additivity in the activation energy.

(b) *Electronic influence of substituents.* In general, the electron-attracting substituents increase the rate of reduction and electron-repelling substituents lower it, the most rapid reactions being shown, for example, by trinitrobenzene and by dinitrobenzoic acid, and the slowest by methyl derivatives of nitrobenzene.

If the rate-determining step is a transfer of electrons from the reducing agent, such an influence is understandable. On the other hand, if the preliminary co-ordination of a

hydrogen ion with the nitro-compound is necessary, as was suggested above, these same influences will operate in the opposite direction. This conflict may well account for the fact that the range of ΔF^* variation is here less than in the benzoylation of amines (Stubbs and Hinshelwood, *J.*, 1949, S 71), the ratio of the rates for the fastest and slowest nitro- or methyl-substituted reactants being there about 10^5 and here less than 10^3.

In general, the usual complex interplay of inductive, electromeric, and steric effects is discernible. Nevertheless, ΔF^* plotted, where possible, for *para*-compounds, $X{\cdot}C_6H_4{\cdot}NO_2$, against the dipole moments of the corresponding C_6H_5X yields a smooth curve (Fig. 6). For the corresponding *ortho*-compounds the curve is irregular but lies generally above that of the *para*-compounds (lower rates corresponding to a fairly general steric retardation), and for the *meta*-compounds the curve is even more irregular.

The greatest acceleration by a single substituent is caused by a *p*-nitro-group, that of an *ortho*-group being smaller presumably as a result of an adverse steric effect. The greatest retardation is observed with *o*-methyl groups where steric and inductive effects combine. Amino-groups behave as electron-attracting groups, being present largely as NH_3^+. The fact that the acceleration is less with the *ortho*- and *para*-groups than with the *meta*-groups is evidently due to the partial compensation by the mesomeric effect (which corresponds to retardation). The action of OCH_3 is mainly mesomeric and correspondingly nearly zero in the *meta*-compound.

Additive Effects of Substituents.—Table 6 shows the changes in ΔF^* caused by single substituents. These values can be used to predict the change in ΔF^* caused by two or more substituents on the assumption of a simple additivity of effect. Table 7 compares these predicted values with the change in ΔF^* from direct rate determinations.

The error in ΔF^* may amount to ± 100 cals. and the error in predicted values can therefore be ± 200 cals. In a large number of cases there is correspondence between the directly determined and predicted values which, though it is less striking than was found in the benzoylation of substituted anilines, is close enough to be significant.

The examples where the additive relation fails most noticeably are with

(p-OH, m-CO_2H); (m-Cl, m-Cl, p-OH); (m-Cl, m-Cl, p-NH_2)

on the one hand, and with

(m-NO_2, m-NO_2); (m-NO_2, m-CO_2H); (m-CO_2H, p-CO_2H)

on the other.

In the first set two groups capable of exerting electromeric effects are adjacent to one another and mutual interference is not surprising. In the dichloronitrophenol for example, there is the possible formation of a chelate ring between Cl and OH (Sidgwick and Callow, *J.*, 1924, **125**, 527) and this might seriously alter the effect which the individual groups normally exert. There may well be interaction between an adjacent OH and CO_2H also. For dichloronitroaniline two chelate rings are possible and it is interesting that this example reveals the greatest discrepancy between directly determined and predicted values.

In the second set the departure from additivity seems to depend upon a certain saturation. Thus with trinitrobenzene there is considerably less than the predicted change in ΔF^*. Here, as in the other two examples quoted, two of the most powerfully acting groups fail to exert the expected effect as though there is a limit to the total amount of disturbance which can be transmitted through the ring and manifested at the seat of reaction.

The authors thank Mr. D. A. Cockerill for his assistance in the early stages of the experimental work.

PHYSICAL CHEMISTRY LABORATORY, OXFORD UNIVERSITY. [*Received, June 8th,* 1953.]

679. *Nucleophilic Displacement Reactions in Aromatic Systems. Part II.* Kinetics of the Reactions of Chloronitropyridines and Chloro-2 : 4-dinitrobenzene with 3- and 4-Picoline.*

By E. A. S. Cavell and N. B. Chapman.

Arrhenius parameters for the reactions in ethanol of chloronitropyridines and chloro-2 : 4-dinitrobenzene with 3- and 4-picoline and with *m*-toluidine are presented. The relative weakness of heterocyclic tertiary amines (cf. Part I *) as nucleophilic reagents towards aromatic chloronitro-compounds is confirmed. It is also concluded that the intervention of ethanolysis in this type of reaction (cf. Bunnett and Zahler, *Chem. Reviews*, 1951, **49**, 273) is unlikely, and that, although the various pairs of reagents may form more or less stable molecular complexes, this is of no great importance to the observed kinetics. The conclusions of Part I concerning the influence of the structure of the halogeno-compound on the Arrhenius parameters are mainly confirmed, but some anomalies have been met. It is also concluded that the influence of methyl groups on the "nucleophilic power" of pyridine bases is what would be expected. The differences between primary aromatic and tertiary heterocyclic amines in the reactions are further discussed in fundamental structural terms.

In Part I * we drew attention to the relatively low rate of displacement of chloride ions from chloronitropyridines by pyridine itself. We now present similar results for 3- and 4-picoline with the object of showing that this phenomenon is normal among heterocyclic tertiary amines, and of elucidating the influence on "nucleophilic power" of alkyl substituents in pyridine. In the discussion which follows we also examine Bunnett and Zahler's suggestion (*Chem. Reviews*, 1951, **49**, 273) that ethanolysis may intervene in reactions of the type we have studied. Also we develop the subject of "nucleophilic power" of pyridine bases. Certain reactions of *m*-toluidine have also been studied for comparison with those of 3-picoline.

Experimental

Materials.—Chloro-compounds and the aqueous ethanol for solvent were prepared as described in Part I.

Amines.—Pyridine was purified as described in Part I. 3- and 4-Picoline were purified by repeated fractionation (150 × 2·5-cm. column packed with Fenske helices) of their azeotropes with acetic acid as described by Coulson and Jones (*J. Soc. Chem. Ind.*, 1946, **65**, 169). Dr. Coulson, The Chemical Research Laboratory, Teddington, kindly determined the purity of the picolines cryoscopically, and reported 99·65 and 99·45 moles % purity for 3- and 4-picoline, respectively. In the reactions studied, these specimens showed no significant differences kinetically from specimens of 99·97 and 99·75% purity kindly supplied by Dr. Coulson. *m*-Toluidine was purified through its acetyl derivative as usual.

Products.—The following *nitro-2-m-toluidinopyridines* obtained are new : 3-nitro-, m. p. 95° (red needles) (Found : C, 62·9; H, 4·8; N, 18·3. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%) ; 5-nitro-, m. p. 128·5° (orange-yellow needles) (Found : C, 62·9; H, 4·6; N, 17·8%).

The quaternary chlorides obtained from the various chloro-compounds and 3- and 4-picoline were difficult to prepare in the pure state, those derived from 4-picoline being particularly prone to decomposition by the combined action of hydroxylic solvents and atmospheric oxygen. They are more readily prepared from solutions of the reactants in boiling anhydrous ether in an atmosphere of nitrogen. In many cases the reaction products from ethereal and from ethanolic solution have been shown to yield identical picrates or styphnates. 1-(3-*Nitro*-4-*pyridyl*)-*pyridinium picrate*, m. p. 185° (Found : C, 45·2; H, 2·3; N, 20·2. $C_{16}H_{10}O_9N_6$ requires C, 44·7; H, 2·3; N, 19·5%). 3-*Methyl*-1-(3-*nitro*-4-*pyridyl*)*pyridinium chloride*, m. p. 197·5° (prepared in dry ether) (Found : C, 52·4; H, 4·4; N, 16·0; Cl, 14·05. $C_{11}H_{10}O_2N_3Cl$ requires C, 52·5; H, 4·0; N, 16·6; Cl, 14·1%), and *picrate*, m. p. 230° (Found : C, 46·3; H, 2·7; N, 18·8. $C_{17}H_{12}O_9N_6$ requires C, 46·0; H, 2·7; N, 18·9%). 4-*Methyl*-1-(3-*nitro*-4-*pyridyl*)-

* Part I, *J.*, 1952, 437.

pyridinium picrate, m. p. 200° (decomp.) (Found: C, 45·9; H, 2·55; N, 19·1%). **3-*Methyl*-1-(3-*nitro*-2-*pyridyl*)*pyridinium styphnate***, m. p. 136° (Found: C, 44·4; H, 2·8; N, 18·4. $C_{17}H_{12}O_{10}N_6$ requires C, 44·4; H, 2·6; N, 18·3%). **3-*Methyl*-1-(5-*nitro*-2-*pyridyl*)*pyridinium picrate***, m. p. 143·5° (Found: C, 46·3; H, 3·0; N, 18·7%). **1-(2 : 4-*Dinitrophenyl*)-4-*methyl*-*pyridinium styphnate***, m. p. 157·5° (Found: C, 42·9; H, 2·3; N, 16·7. $C_{18}H_{12}O_{12}N_6$ requires C, 42·9; H, 2·4; N, 16·7%).

TABLE 1.

Reactions of 3-*picoline.*

2-*Chloro*-5-*nitropyridine at* 60·0°.

(*A*) Amine 0·400M, chloro-compound 0·100M.

Time (min.) ...	1350	2450	3150	3950	5350	6950	9800	14,100
Decompn. (%)	16·9	28·6	35·1	41·6	51·8	61·3	73·5	84·7
$k \times 10^5$	5·83	5·93	5·95	6·00	6·10	6·23	6·37	6·43

Mean $k = 6{\cdot}10 \pm 0{\cdot}18 \times 10^{-6}$; 50% decompn. at 5097 min.

(*B*) With half the above concns.; mean $k = 5{\cdot}88 \pm 0{\cdot}19 \times 10^{-6}$; 50% decompn. at 10,570 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}07$.

4-*Chloro*-3-*nitropyridine at* 30·0°.

(*A*) Amine 0·400M, chloro-compound 0·100M.

Time (min.) ...	1400	2500	3900	5460	7170	8840	12,910
Decompn. (%)	15·9	26·4	38·0	48·5	58·2	65·7	78·8
$k \times 10^6$	5·35	5·38	5·50	5·57	5·67	5·75	5·93

Mean $k = 5{\cdot}59 \pm 0{\cdot}16 \times 10^{-6}$; 50% decompn. at 5610 min.

(*B*) With half the above concns.: mean $k = 5{\cdot}43 \pm 0{\cdot}25 \times 10^{-6}$; 50% decompn. at 11,440 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}03$.

Reactions of 4-*picoline.*

Chloro-2 : 4-*dinitrobenzene at* 40·0°.

(*A*) Amine 0·400M, chloro-compound 0·100M.

Time (min.) ...	820	1150	1500	2190	2620	3750	5150	10,920
Decompn. (%)	16·8	21·8	27·3	36·3	43·1	54·6	65·1	86·7
$k \times 10^5$	9·82	9·22	9·48	9·32	9·85	9·88	9·85	9·73

Mean $k = 9{\cdot}64 \pm 0{\cdot}23 \times 10^{-6}$; 50% decompn. at 3297 min.

(*B*) With half the above concns.: mean $k = 9{\cdot}15 \pm 0{\cdot}12 \times 10^{-6}$; 50% decompn. at 6795 min. $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2{\cdot}06$.

TABLE 2.*

Amine	50·0° (i)	50·0° (ii)	60·0° (i)	60·0° (ii)	70·0° (i)	70·0° (ii)
	2-Chloro-3-nitropyridine					
3-Picoline	13·5—76·0	1·15—1·21	16·4—80·1	2·72—2·88	14·1—85·3	6·15—6·62
4-Picoline	12·8—79·5	1·90—2·10	14·8—85·1	4·53—4·87	16·1—86·2	9·83—10·72
m-Toluidine	15·2—78·5 †	15·5—16·7	15·1—83·5	31·0—32·7	—	—
	40·0°		50·0°		60·0°	
	2-Chloro-5-nitropyridine					
3-Picoline	12·5—82·9 ‡	1·04—1·12 ‡	17·2—69·7	2·52—2·72	16·9—84·7	5·83—6·43
4-Picoline	14·2—87·2 ‡	1·63—1·72 ‡	11·8—86·4	3·87—4·05	15·8—90·5	8·98—9·27
m-Toluidine	18·2—76·5	5·77—6·50	18·5—84·9	11·0—12·7	29·0—74·1	2·03—2·20
	20·0°		30·0°		40·0°	
	4-Chloro-3-nitropyridine					
3-Picoline	15·1—85·2	2·30—2·48	15·9—78·7	5·35—5·93	17·0—75·4	12·6—13·7
4-Picoline	21·7—87·9	4·05—4·28	15·5—75·4	9·27—10·2	14·7—75·9	20·8—23·3
	30·0°		40·0°		50·0°	
	Chloro-2 : 4-dinitrobenzene					
3-Picoline	14·9—80·9	2·18—2·40	12·1—73·9	5·28—5·67	16·4—78·6	12·6—13·5
4-Picoline	12·3—83·7	3·90—4·10	16·8—86·7	9·22—9·88	18·5—85·1	21·8—23·8

* Usually $a = 0{\cdot}4$M, $b = 0{\cdot}1$M. ‡ Temp. 39·9°.

(i) Extreme values of percentage decompn. (ii) Extreme values of $k \times 10^6$. (For mean k's at 55° see Table 3.)

† At 40°: (i) 15·4—80·5, (ii) 7·57—7·82.

Procedure.—This was the same as in Part I, the method of sealed bulbs being used, and all experiments were carried out at least in duplicate. Independently determined values of k (mean of a series in a given experiment) rarely differed by more than 1%. The position in respect of solvolysis and autocatalysis was as in Part I.

Results.—Detailed values for some of the reactions are given in Table 1 and all the results are summarised in Table 2. For primary amines

$$k = \frac{1}{2t(0{\cdot}5a - b)} 2{\cdot}303 \log_{10} \frac{b}{0{\cdot}5a} \cdot \frac{0{\cdot}5a - x}{b - x}$$

and for tertiary amines

$$k = \frac{1}{t(a - b)} 2{\cdot}303 \log_{10} \frac{b}{a} \cdot \frac{a - x}{b - x}$$

where a is the initial concn. of base and b that of the chloro-compound. The experimentally observed times are recorded in minutes, but velocity coefficients are given in the usual units, *viz.*, l. mole^{-1} sec.$^{-1}$. Errors in k given after the $\pm$ sign are mean deviations from the mean. Temperatures are accurate to $\pm 0{\cdot}03°$.

TABLE 3.

Reaction no.	Amine	Chloro-compound	$k^{55} \times 10^6$	E (cal.)	$\log_{10} A$
1	Pyridine	2-Chloro-3-nitropyridine	1·03	18,700	6·3
2	3-Picoline	,,	1·81	18,500	6·6
3	4-Picoline	,,	3·15	17,400	6·1
5	*m*-Toluidine	,,	22·4	14,400	5·0
6	Pyridine	2-Chloro-5-nitropyridine	1·97	18,100	6·3
7	3-Picoline	,,	4·00	17,900	6·6
8	4-Picoline	,,	6·11	17,500	6·5
9	*m*-Toluidine	,,	15·8	12,900	3·8
10	Pyridine	4-Chloro-3-nitropyridine	32·1	16,900	6·8
11	3-Picoline	,,	39·8	15,600	6·0
12	4-Picoline	,,	66·4	15,100	5·9
13	Pyridine	1-Chloro-2 : 4-dinitrobenzene	11·1	16,700	6·2
14	3-Picoline	,,	19·9	17,100	6·7
15	4-Picoline	,,	30·9	16,900	6·7

Values of k are usually accurate to $\pm 3\%$, of E to ± 300 to ± 500 cal., of $\log A$ to $\pm 0{\cdot}3$—$0{\cdot}5$ unit.

DISCUSSION

Intervention of Ethanolysis.—Bunnett and Zahler (*loc. cit.*) have suggested that there may be a concurrent ethanolysis in reactions such as those under discussion because of equilibria of the type $R_3N + EtOH \rightleftharpoons R_3HN^+ + EtO^-$ (i). Reaction (ii) may then compete with (iii) or (iv) according to the nature of the amine:

$$R'X + EtO^- \longrightarrow R'OEt + X^- \quad \text{(ii)}$$

$$R'X + R_3N \longrightarrow R'R_3N^+ + X^- \quad \text{(iii)}$$

$$R'X + 2R_2NH \longrightarrow R_2NR' + R_2H_2N^+ + X^- \quad \text{(iv)}$$

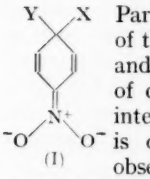
On consideration of reactions (ii) and (iii) it is easily seen that $dx/dy = k_3/k_2\{[R_3N]/[EtO^-]\}$, where y and x are the values of $[X^-]$ at time t due to (ii) and (iii) respectively, and k_2 and k_3 are corresponding rate coefficients. Remembering that $K_b/[R_3HN^+] = [EtO^-]/[R_3N]$ from (i), we have $dx/dy = k_3/k_2\{[R_3HN^+]/K_b\}$. To a close approximation $[R_3HN^+] = y$, whence $dx/dy = k_3y/k_2K_b$, and $y = (2K_bk_2x/k_3)^{\frac{1}{2}}$. For the reaction of chloro-2 : 4-dinitrobenzene with pyridine in ethanol at 25°, K_b is $5{\cdot}6 \times 10^{-15}$ (Goldschmidt and Mathiesen, *Z. phys. Chem.*, 1926, **119**, 447; Danner, *J. Amer. Chem. Soc.*, 1922, **44**, 2832), k_3 is $8{\cdot}4 \times 10^{-7}$ l. mol.$^{-1}$ sec.$^{-1}$ (Part I), and k_2 is $12{\cdot}5 \times 10^{-2}$ l. mol.$^{-1}$ sec.$^{-1}$ (Baudet, *Rec. Trav. chim.*, 1924, **43**, 707), whence $y = 4 \times 10^{-5}x^{\frac{1}{2}}$. Thus in this case ethanolysis is negligible. Data are not available for calculating K_b at other temperatures, but from corresponding values for aqueous solutions and the appropriate energies of activation, it seems unlikely that the above conclusion would be substantially different at any of the temperatures used in this work. Although appropriate values of k_2 are not available for the reactions of chloronitropyridines, Mangini and Frenguelli's results (*Gazzetta*, 1939, **69**, 86) make similar conclusions almost certain for these reactions.

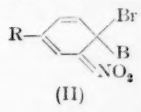
We now consider reactions of type (iv), in which the use of strongly basic secondary amines may cause ethanolysis. Now $dx/dy = k_1/k_2\{[R_2H_2N^+]/K_b\}$, and to a close approximation $[R_2H_2N^+] = (x + y)$, whence $dx/dy = k_1/k_2K_b\{(x + y)\}$, which gives on integration $x = e^{cy}/c - (y + c^{-1})$ where $c = k_1/k_2K_b$, whence $y = c^{-1} \ln\{c(x + y + c^{-1})\}$.

Consider, as an example, piperidine in reaction with chloro-2 : 4-dinitrobenzene. K_b for piperidine in ethanol at 25° is $\sim 10^{-7}$ (Ogston, *J.*, 1936, 1023), and is unlikely to exceed 10^{-6} even at 100°, while the ratio k_2/k_1 is ~5 for 25° (Bunnett *et al.*, *loc. cit.*, p. 340) and increases to ~25 at 100°. We take 10^5 as a representative value of c, and when $(x + y)$ is 10^{-2}, *i.e.*, at 10% "apparent reaction," an approximate calculation shows that x/y is ~140. Moreover, at n% "apparent reaction," $\alpha_n = (v_2/v_4)_n = k_2[EtO^-]_n/k_4[R_2NH]_n = \{c[R_2H_2N^+]\}^{-1}$. To a close approximation $[R_2H_2N^+] = 0{\cdot}01nm$, where m is the initial molarity of R'X, in our work usually 0·1. Hence, putting $c = 10^5$, we have $\alpha_n = 10^{-2}n^{-1}$. Hence, even with strongly basic amines at up to 100°, the rate of ethanolysis becomes negligible compared with that of the main reaction as soon as n exceeds a few units. Therefore by taking an appropriate zero of time the effect of ethanolysis can be eliminated entirely.

Reversibility.—We have found no evidence of a "readily reversible attack" by pyridine or its homologues on chloro-2 : 4-dinitrobenzene mentioned by Leahy and Miller (*Chem. and Ind.*, 1953, 40). The corresponding pyridinium salt loses not more than 0·5% of its chloride ion after one month in ethanol at 40°, and in all the reactions we have studied, after about 30 times the half-life, chloride-ion titrations correspond to 99·0—100·0% reaction.

Aromatic Nucleophilic Substitution.—Bunnett and Zahler (*loc. cit.*) make the fundamental assumption that *all* nitro-activated substitutions "proceed through intermediates of some stability" which are formulated as in (I). One of us (Chapman and Parker, *J.*, 1951, 3301) has argued against this assumption, and recent studies of the molecular complexes formed by aniline and *m*-dinitrobenzene (Landauer and McConnell, *J. Amer. Chem. Soc.*, 1952, **74**, 1221) suggest that the formation of complexes is not due to covalent-bond formation but to "an acid–base interaction" (cf. Mulliken, *ibid.*, p. 811) and that the geometry of the complex is quite different from that required by (I). Preliminary spectroscopic observations in these laboratories (B. Capon, unpublished) indicate that, for α-naphthylamine and for aniline, equilibrium in complex formation with chloro-2 : 4-dinitrobenzene is rapidly attained, and that if the substitution process involves a complex of type (I), the anionisation of the halogen is probably rate-determining. Despite Berliner and Monack's arguments (*ibid.*, p. 1578), it is very difficult to understand the facilitating effect of additional *o*- and *p*-nitro-groups on nucleophilic substitution, in terms of a rate-determining anionisation of halogen. Also, Francel's spectroscopic observations (*ibid.*, p. 1268) confirm the suggestion that a nitro-group *ortho* to halogen is not coplanar with the ring, so its influence on electron density at the seat of substitution is mainly inductive, a point overlooked by Berliner *et al.* (*loc. cit.*). Complexes of type (II) (*idem*, *ibid.*) are also rendered improbable. However, we await the results of *X*-ray crystallographic studies on *o*- and *p*-chloronitrobenzene before coming to a conclusion on this point, and assume a one-stage bimolecular process for these reactions.


(I)


(II)

Influence of the Structure of the Halogeno-compound on the Parameters of the Arrhenius Equation.—The results assembled in Table 3 mainly confirm in broad outline the conclusions reached in Part I (*loc. cit.*, p. 445). Replacement of a nitro-group *ortho* to the seat of substitution by a cyclic nitrogen atom always increases E by 400—800 cal., log A remaining almost constant. Moving the nitro-group from the 5- to the 3-position in 2-chloropyridine usually increases E by ~600 cal., but reactions of 4-picoline are anomalous in this respect. Consideration of the reactions of pyridine only, leads to an oversimplification of the facilitating influence of a "*para*" cyclic nitrogen atom on nucleophilic displacement, for comparison of reactons 11 and 13, and 12 and 14, suggests that the cyclic nitrogen atom is more effective than a nitro-group in diminishing the value of E, although, as this is associated with a diminution of log A in the same sense, specific rates

are not so strongly affected and structural interpretations are largely precluded. The reactions of 4-chloro-3-nitropyridine with 3- and 4-picoline appear from the values of E and log A to be characterised by a degree of solvation in the transition state unusually high among this group of reactions.

Nucleophilic Power of Pyridine Bases.—The weakness of these bases as nucleophilic reagents relative to corresponding primary aromatic amines with considerably smaller basic dissociation constants in aqueous solution at 25°, is amply confirmed by the results of Tables 3 and 4, and those given in Part I. Moreover, we are now able to elucidate the influence of methyl substituents on the nucleophilic power of pyridine bases. Relevant experimental results are assembled in Table 4, in which reactions of 2-chloro-5-nitropyridine are considered, as these are least complicated.

TABLE 4.

Base	$-$ og K_b (25° in H_2O)	ΔH° (cal./mole)	$-\Delta S^\circ$ (cal./° K)	$-$ log k (25°)	E (cal./mole)	log A
Aniline	9·42 [1]	6100	22·8	5·80	13,100 [3]	3·8 [3]
m-Toluidine ...	9·31 [1]	5900	22·8	5·66	12,900	3·8
p-Toluidine	8·93 [1]	5300	23·2	5·34	12,700 [3]	3·9 [3]
Pyridine	8·84 [2]	8700	11·0	6·89	18,100	6·3
3-Picoline	8·34 [2]	8100	—	6·61	17,900	6·6
4-Picoline	7·97 [2]	7500	—	6·39	17,500	6·5

[1] Calculated from values given by Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3468. [2] Herington, *Discuss. Faraday Soc.*, 1950, No. 9, 26. [3] Part I, p. 443.

Values of K_b for ethanolic solution are not available for pyridine bases, but the values for aqueous solution are usually greater by a constant factor of $\sim 10^4$ (Goodhue and Hixon, *J. Amer. Chem. Soc.*, 1934, **56**, 1329). There is an empirical correlation between the heat of ionisation of the bases in aqueous solution and the energy of activation of their reactions with 2-chloro-5-nitropyridine in ethanol: a similar trend is also noticeable for the reactions of 2-chloro-3-nitropyridine, but those of 4-chloro-3-nitropyridine and those of chloro-2 : 4-dinitrobenzene are anomalous (cf. p. 3392). It is concluded that methyl groups in the 3- or the 4-position exert the same kind of influence in primary aromatic and tertiary heterocyclic amines, *viz.*, electron accession to the nitrogen atom by induction from the 3-position, and induction and hyperconjugation from the 4-position.

In our previous discussion of the differences between primary aromatic and tertiary heterocyclic amines as nucleophilic reagents one feature has been neglected. The nitrogen atom in pyridine is in the sp^2 hybridised state and remains so on protonation (cf. Coulson, "Valence," Oxford, 1952, p. 240), and probably remains so in any process of "quaternisation." In aniline, however, the conjugation of the amino-group with the ring demands that the nitrogen atom be more or less sp^2 hybridised (cf. ammonia) but on protonation or "quaternisation" a change to sp^3 hybridisation occurs, and an electron pair, formerly occupying a delocalised orbital formed by overlap of a p orbital of nitrogen with a π orbital of the ring, enters a localised molecular orbital formed by overlap of a sp^3 hybridised orbital of nitrogen and a suitable orbital of hydrogen or carbon.

One important feature of attaining the transition state in the "quaternisation" of pyridine or aniline is energy liberated by partial formation of the new bond. This will differ for the two systems because of the differences outlined above, and from the graph given by Coulson (*Proc. Roy. Soc.*, 1951, *A*, **207**, 67), admittedly applying to two carbon atoms rather than a carbon and a nitrogen atom, it seems that this energy would not be less for reactions of pyridine. For aniline, however, attainment of the transition state also involves partial loss of the "additional resonance energy" (cf. Coulson, *op. cit.*, p. 247), variously estimated at 3—6 kcal. per mole. It is probable that neither of these factors will facilitate the reactions of aniline and similar primary amines relatively to those of pyridine. However, consideration of the entropies of activation suggests that solvation of the transition state is stronger for primary than for tertiary amines, and this, together with the "net *ortho*-effect" discussed in Part I, is probably the cause of the observed differences in Arrhenius parameters.

Finally, it is noteworthy that the scanty evidence in the literature on kinetics of

analogous reactions of pyridine and aniline (cf. Baker, *J.*, 1932, 1148, 2631; 1933, 1128) suggests that, on the whole, very marked differences between primary aromatic and tertiary heterocyclic amines as nucleophilic reagents are not observed in reactions with phenacyl halides, thus reinforcing our view of the importance of an *ortho*-nitro-group in the halogeno-compound in accounting for the differences we have observed.

We thank the Chemical Society for a grant for materials, Imperial Chemical Industries Limited for a grant for microanalyses and materials, and Dr. E. A. Coulson, The Chemical Laboratory, Teddington, for the supply of pure samples of 3- and 4-picoline, and for assaying our own samples.

THE UNIVERSITY, SOUTHAMPTON. [*Received, June 11th*, 1953.]

680. *Methods for Computing Successive Stability Constants from Experimental Formation Curves.*

By H. IRVING and (MRS.) H. S. ROSSOTTI.

Attention is drawn to the approximations implicit in existing methods for computing, from experimental data, the successive stability constants governing the formation of complexes in step-equilibria. A new " correction term " method is described. This makes use of the symmetry properties of the formation curve for the particular case $N = 2$.

The problem of computing the " best " set of stability constants from inconsistent experimental data is shown to be soluble by a least-squares treatment after an algebraic transformation. This procedure is applicable to systems of higher complexity. The effects of improved methods of computation are illustrated by examples taken from the literature.

Note on Symbolism.—Following Bjerrum most authors have used k_n to represent the stability constant of a complex ML_n relative to ML_{n-1}. Schwarzenbach uses K_{ML_n}. Now K is customarily used for equilibrium constants, and k for velocity constants, and to avoid confusion we shall use K_n for the above stability constant. The overall constant $[ML_n]/[M][L]^n$ (see p. 3399) has been variously designated $\overline{K}^{L}_{ML_n}$ (Schwarzenbach), K_n (Bjerrum), and β_n (Fronaeus and other Scandinavian authors). We prefer the last, so that the expression $\beta_n = K_1K_2K_3 \ldots K_n$ in our terminology corresponds to $K_n = k_1k_2k_3 \ldots k_n$ in Bjerrum's.

THE formation of a complex species ML_n from a central atom or ion M, and molecules or ions of a *ligand* L, is assumed to be governed by a series of thermodynamic equilibrium constants defined by

$$K_n^T = \{ML_n\}/\{ML_{n-1}\}\{L\} = K_n/F_n$$

where K_n is the classical (concentration) equilibrium constant, $F_n = f_{ML_{n-1}} \cdot f_L/f_{ML_n}$, and charges are omitted for the sake of generality. If L is uncharged, ML_n and ML_{n-1} carry the same ionic charge, so that, provided measurements are made in solutions of constant, and not too high, ionic strength, F_n may be set equal to unity, and the convenient approximation $K_n \cong K_n^T$ is valid. Bjerrum (*Kgl. Danske Videnskab. Selsk.*, 1946, **22**, Nr. 18) used a single average value of F_n in his studies of complexes formed by cupric and chloride ions. The same author (" Metal Ammine Formation in Aqueous Solution," P. Haase, Copenhagen, 1941) introduced the concept of the *degree of formation*, or ligand number, $\bar{n}$, which he defined as the average number of ligand molecules or ions per molecule of M, and showed that for all systems in which only mononuclear complexes occur, values of $\bar{n}$, and of [L], the concentration of free ligand, are related by the equation

$$\sum_{n=0}^{n=N} (\bar{n} - n)\beta_n[L]^n = 0 \quad \ldots \ldots \ldots \quad (1)$$

where $\beta_n = K_1K_2 \ldots K_n$, and $\beta_0 = 1$, by definition.

Experimental methods for the determination of stability constants, developed by Leden, Bjerrum, and Fronaeus, have recently been discussed by Sullivan and Hindman

(*J. Amer. Chem. Soc.*, 1952, **74**, 6091), who point out that sets of equations of the type (1) can be solved for unique, non-trivial values of K_1, K_2, and K_n if the determinant

$$\begin{vmatrix} (\bar{n}_1 - 1)[L_1] + \ldots (\bar{n}_N - N)[L_1]^N \\ (\bar{n}_1 - 1)[L_N] + \ldots (\bar{n}_N - N)[L_N]^N \end{vmatrix} \neq 0$$

This expresses the condition that N inhomogeneous equations of the type (1) are needed for the evaluation of N stability constants in systems where the highest complex has the formula ML_N. In practice, experimental data exceed these minimal requirements, and the real problem is to find those values for the constants, k_n, which will best represent all the experimental results. Two difficulties arise. (i) The substitution of experimentally determined values of $\bar{n}$ and [L] into (1) will give a set of $m > N$ equations which will probably be inconsistent owing to experimental errors. (ii) The data obtained experimentally may not be fully representative of the whole function. As a particular case, linear equations formed from neighbouring points may be ill-conditioned. The present paper deals with this problem of obtaining the best set of stability constants from experimental values of $\bar{n}$ and [L], and will be restricted to systems for which $N = 2$ and the equation

$$\bar{n} + (\bar{n} - 1)K_1[L] + (\bar{n} - 2)K_1K_2[L]^2 = 0 \quad . \quad . \quad . \quad . \quad (2)$$

is applicable.

The current methods for obtaining K_1 and K_2 from the formation curve are discussed below, as the limitations and assumptions underlying the calculations do not always seem to be fully appreciated. Additional methods for computing stability constants are suggested, and applied to some formation curves in the literature. The present object is to compute the best stability constants from experimental data, rather than to discuss the significance of the values so obtained, or the quality of the experimental work.

Method A. Successive Approximations.—From equation (2), we have

$$K_1 = \frac{1}{[L]} \cdot \frac{\bar{n}}{(1 - \bar{n}) + (2 - \bar{n})K_2[L]} \quad . \quad . \quad . \quad . \quad . \quad . \quad (3a)$$

and

$$K_2 = \frac{1}{[L]} \cdot \frac{\bar{n} + (\bar{n} - 1)K_1[L]}{(2 - \bar{n})K_1[L]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3b)$$

which emphasise that the calculation of K_1 depends on the value of K_2 and *vice versa*. Bjerrum (*op. cit.*, p. 37) applies these equations to the refinement by successive approximations of "temporary" constants obtained by other methods. If n experimental points determine the formation curve, there are $m(m - 1)/2$ pairs of values which could be treated in this way; but some judgment would be necessary since several combinations would yield ill-conditioned equations and the resulting values of K_1 and K_2 would have to be omitted from the general average.

Method B. Solution of Simultaneous Equations.—When $N = 2$, the required stability constants can be obtained by solving pairs of simultaneous equations derived from (2). The criticisms of Method A apply equally here.

Method C. Interpolation at Half $\bar{n}$ *Values.*—From equations (3*a*) and (3*b*) we have

$$\log K_1 = pL_{1/2} + \log [2/(1 + \sqrt{1 + 12K_2/K_1})] \quad . \quad . \quad . \quad . \quad (4a)$$

and

$$\log K_2 = pL_{3/2} - \log [2/(1 + \sqrt{1 + 12K_2/K_1})] \quad . \quad . \quad . \quad . \quad (4b)$$

where pL_a represents the free ligand exponent when $\bar{n} = a$. Provided that $K_{n-1} \gg K_n$, approximately equal amounts of ML_{n-1} and ML_n will be present in solution when $\bar{n} = n - \frac{1}{2}$, and the contributions of ML_{n-2} and ML_{n+1} may be neglected. Following Bjerrum (*op. cit.*, p. 36) we may write

$$\log K_n = pL_{n-\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Unless $K_1/K_2 \geqslant 10^{2.5}$, this very commonly used approximation can introduce considerable error (see p. 3404), and in the case where $N = 2$ it has the disadvantage of using only two points on the formation curve.

Method D. Interpolation at Various $\bar{n}$ *Values.*—Rewriting equation (2) for the point $(pL_{1-d}, 1-d)$, we have

$$\log K_1 = pL_{1-d} + \log \{2(1-d)/[d + \sqrt{d^2 + 4(1-d^2)k_2/k_1}]\} \quad . \quad (7)$$

which reduces to

$$\log K_1 = pL_{1-d} + \log [(1-d)/d] \quad . \quad . \quad . \quad . \quad . \quad . \quad (8a)$$

when $K_1 \gg K_2$. Similarly,

$$\log K_2 = pL_{1+d} - \log [(1-d)/d] \quad . \quad . \quad . \quad . \quad . \quad . \quad (8b)$$

The use of these equations over the whole range of the formation curve ($0<d<1$) is only justified if $K_1/K_2 > 10^4$, though in this case Method D is preferable to Method C as it can be applied at several points along the formation curve, and the mean values of K_1 and K_2 obtained from the results. If $K_1/K_2 < 10^4$, calculated values of stability constants show a drift which is more pronounced the lower the value of d. Albert (*Biochem. J.*, 1950, **47**, 531) averages constants obtained in this manner. Jonassen, LeBlanc, and Rogan (*J. Amer. Chem. Soc.*, 1950, **72**, 4960) take the most probable value to be that obtained from the point where $d = \frac{1}{2}$; this is, in effect, employing Method C.

Method E. Use of the Mid-point.—(i) At the mid-point of the formation curve, where $\bar{n} = 1$

$$K_1K_2[L_1]^2 = 1, \text{ or } \log K_1K_2 = 2pL_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

The abscissa of the mid-point will therefore give a value for the overall constant β_2 whose precision is limited only by that of the experimental measurements. The common practice of evaluating individual values of K_1 and K_2 from the product K_1K_2 so obtained, together with equation (5), demands a full appreciation of the implicit approximations, and does not make full use of the experimental data.

(ii) For a system in which $N = 2$, Bjerrum (*op. cit.*, p. 24) defines a spreading factor, $x = \sqrt{K_1/4K_2}$, and relates it to the mid-point slope, D, of the formation curve at the point where $\bar{n} = 1$ by the expression $D = -2{\cdot}303/(1 + x)$. From the measured mid-point slope the ratio K_1/K_2 may be calculated, and individual values of K_1 and K_2 obtained from this and equation (9). This method is only applicable where K_1/K_2 lies between 10^3 and 10^{-2} (as $K_1/K_2 \longrightarrow \infty$, $D \longrightarrow 0$, and as $K_1/K_2 \longrightarrow 0$, $D \longrightarrow -2{\cdot}303$) and it uses only a very small portion of the formation curve in the region of the mid-point. Significant errors may be introduced both in plotting the " best " formation curve to pass through the experimental points, and in measuring its mid-point slope.

Method F. Schwarzenbach's Graphical Method.—Schwarzenbach, Willi, and Bach (*Helv. Chim. Acta*, 1947, **30**, 1303) described a graphical method for computing the dissociation constants of dibasic acids from data obtained by potentiometric titrations; this was later applied to the computation of stability constants of metal complexes (Schwarzenbach and Ackerman, *ibid.*, 1948, **31**, 1029).

Their method can be adapted to the computation of stability constants from experimental values of $\bar{n}$ and [L] by plotting values of $A = (\bar{n} - 1)[L]/\bar{n}$ and $B = (\bar{n} - 1)/(2 - \bar{n})[L]$ as abscissæ and ordinates respectively. All lines passing through pairs of points (A, B) should intersect when extrapolated at the point $(1/K_1, K_2)$. This procedure is unreliable if lengthy extrapolation is necessary and is only suited to experimental data of high precision.

General Comments.—It will have been seen that the choice of computational method depends on the ratio K_1/K_2 in the system under consideration. An approximate value of this ratio may rapidly be obtained from the mid-point slope, D, of the formation curve, without introducing the concept of the spreading factor. For systems in which $N = 2$, D is given by

$$D = -4{\cdot}606/(2 + \sqrt{K_1K_2})$$

and values of D for given K_1/K_2 ratios are given in Table 1. Thus, if Method C is to be used, K_1/K_2 must be $>10^{2{\cdot}5}$, and D must be $> -0{\cdot}23$. The formation curve is then wave-like. For Method D, K_1/K_2 must be $>10^4$, and D must be $> -0{\cdot}04$, giving rise to a formation curve showing two very distinct steps. Method E is applicable to systems where $10^{-2} < K_1/K_2 < 10^3$, and $-2{\cdot}2 < D < -0{\cdot}14$. It is seen that, in the " normal " case, where

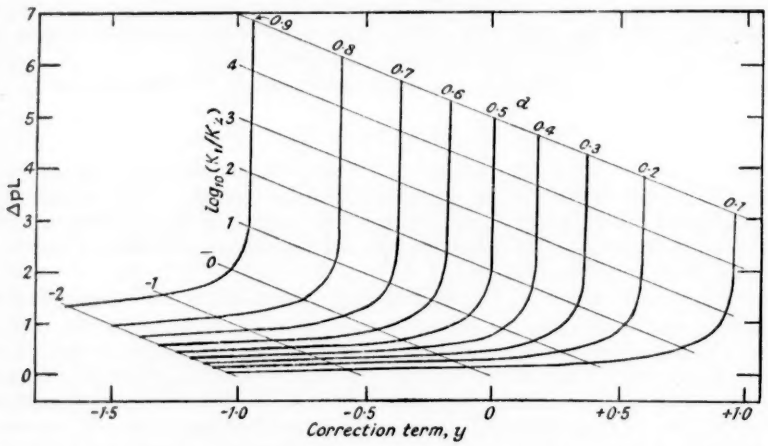
$K_1 > K_2$, $0 > D > -1{\cdot}535$, while if $K_2 > K_1$ (*e.g.*, for the complex ammines of Ag^+ in water) $-1{\cdot}535 > D > -2{\cdot}303$.

TABLE 1. *The mid-point slope*, D, *for systems in which* N = 2.

$\log K_1/K_2$	5	4	3	2	1	0
D	−0·0145	−0·0451	−0·137	−0·384	−0·892	−1·535
$\log K_1/K_2$	−1	−2	−3	−4	−5	$-\infty$
D	−1·989	−2·193	−2·267	−2·292	−2·300	−2·303

Additional Methods for Computing Stability Constants.—The ideal method should minimise the subjective "smoothing" implicit in most graphical procedures and ought to employ the experimental data as fully as possible. The two new methods presented below do not fully attain this ideal, but represent a real improvement on existing ones.

FIG. 1. *Correction terms.*



Method G. "Correction-term" Method.—In a system where $N = 2$, the theoretical formation curve is symmetrical about its mid-point so that from (8) and (9)

$$pL_{1-d} + pL_{1+d} = 2pL_1 = \log K_1K_2 \quad . \quad . \quad . \quad . \quad . \quad (10)$$

From (7),

$$\log K_1 = pL_{1-d} + y \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11a)$$

and

$$\log K_2 = pL_{1+d} - y \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11b)$$

where the "correction term," y, is given by

$$y = \frac{2(1-d)}{d + \sqrt{d^2 + 4(1-d^2) \cdot K_2/K_1}} \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

and depends in magnitude both upon d and upon the ratio K_2/K_1. If $K_1/K_2 > 10^4$, equation (12) reduces to $y \cong \log [(1-d)/d]$, and the correction term depends only on the value of d (Method D) and becomes zero in the special case where $d = \frac{1}{2}$ (Method C).

If pL_{1-d} and pL_{1+d} are two points on the formation curve disposed symmetrically about the mid-point, then from equations (10) and (11)

$$\Delta pL_d = pL_{1-d} - pL_{1+d} = \log(K_1/K_2) + 2y \quad . \quad . \quad . \quad . \quad (13)$$

By using equations (12) and (13), corresponding values of y and ΔpL have been calculated for nine values of d for each of a series of values of K_1/K_2 ranging from 10^5 to 10^{-2}. The relationship between y and ΔpL is shown graphically in Fig. 1, but full advantage of the method can only be taken if this is drawn on a much larger scale, for which the necessary data are given in Table 2.

The correction-term method is applied as follows to pairs of values ($\bar{n}$, pL) symmetrically disposed about the mid-point. Suppose the experimental values were $pL_{0.4} = 9.50$ and $pL_{1.6} = 8.00$. The value of the correction term, $y(= -0.23)$, is read off from the curve for $d = 0.6$ as abscissa corresponding to $\Delta pL = 1.50$. Thence $\log K_1 = 9.50 - 0.23 = 9.27$, and $\log K_2 = 8.00 + 0.23 = 8.23$. The process is repeated for several values of d and the mean value of the calculated stability constants is taken. In practice, it is convenient to draw the best formation curve through the experimental points and to read off values of $pL_{1 \pm d}$ for those values of d tabulated. Although this involves some " smoothing " of the experimental data, the correction-term procedure is very rapid and reliable as it takes fully into account the complicating factors introduced by the absolute magnitude of the ratio K_1/K_2 which may vitiate the application of Methods C and D. On the other hand, small changes in ΔpL correspond to large changes in y when the ratio K_1/K_2 becomes low (cf. Table 2). This is especially marked in the central part of the curve, and if $K_1 < K_2$, values calculated from d smaller than 0·5 will not be reliable.

TABLE 2. *The relationship between* y *and* pL *for several values of* d.

	$d = 0.1$		$d = 0.2$		$d = 0.3$		$d = 0.4$		$d = 0.5$	
$\log K_1/K_2$	y	ΔpL	y	ΔpL	y	ΔpL	y	ΔpL	y	ΔpL
5·000	0·954	3·092	0·602	3·796	0·368	4·264	0·176	4·648	0·000	5·000
4·000	0·954	2·092	0·602	2·796	0·368	3·264	0·176	3·648	0·000	4·000
3·523	0·942	1·639	0·599	2·325	0·366	2·789	0·175	3·173	0·000	3·523
3·000	0·916	1·167	0·592	1·816	0·364	2·272	0·174	2·652	−0·001	3·003
2·523	0·861	0·802	0·574	1·376	0·355	1·812	0·169	2·185	−0·004	2·531
2·000	0·746	0·507	0·523	0·954	0·330	1·341	0·158	1·684	−0·012	2·025
1·523	0·593	0·336	0·430	0·663	0·273	0·976	0·120	1·283	−0·035	1·592
1·000	0·388	0·225	0·274	0·452	0·159	0·682	0·036	0·928	−0·094	1·188
0·523	0·178	0·167	0·093	0·336	0·004	0·515	−0·085	0·693	−0·196	0·916
0·000	−0·065	0·130	−0·131	0·262	−0·202	0·405	−0·278	0·556	−0·362	0·725
−0·477	−0·296	0·116	−0·354	0·231	−0·413	0·349	−0·477	0·477	−0·549	0·621
−1·000	−0·551	0·101	−0·602	0·204	−0·656	0·312	−0·715	0·430	−0·778	0·556
−1·477	−0·786	0·095	−0·835	0·193	−0·885	0·294	−0·940	0·402	−1·000	0·523
−2·000	−1·046	0·091	−1·092	0·184	−1·141	0·282	−1·193	0·287	−1·251	0·502

	$d = 0.6$		$d = 0.7$		$d = 0.8$		$d = 0.9$	
$\log K_1/K_2$	y	ΔpL	y	ΔpL	y	ΔpL	y	ΔpL
5·000	−0·176	5·352	−0·368	5·736	−0·602	6·205	−0·954	6·908
4·000	−0·176	4·352	−0·368	4·736	−0·602	5·205	−0·954	5·908
3·523	−0·176	3·876	−0·368	4·260	−0·602	4·727	−0·954	5·431
3·000	−0·177	3·354	−0·368	3·737	−0·602	4·204	−0·954	4·909
2·523	−0·178	2·880	−0·369	3·261	−0·603	3·728	−0·954	4·432
2·000	−0·184	2·367	−0·372	2·745	−0·604	3·209	−0·955	3·910
1·523	−0·198	1·918	−0·381	2·285	−0·609	2·741	−0·957	3·437
1·000	−0·238	1·477	−0·407	1·815	−0·615	2·230	−0·964	2·928
0·523	−0·317	1·158	−0·465	1·452	−0·662	1·846	−0·980	2·482
0·000	−0·459	0·917	−0·582	1·164	−0·749	1·497	−0·032	2·064
−0·477	−0·633	0·789	−0·736	0·996	−0·879	1·281	−1·123	1·770
−1·000	−0·852	0·705	−0·944	0·887	−1·066	1·133	−1·279	1·557
−1·477	−1·069	0·661	−1·154	0·831	−1·268	1·060	−1·459	1·441
−2·000	−1·317	0·634	−1·398	0·796	−1·506	1·012	−1·680	1·359

The value of the correction term, y, may also be calculated from the exact equation

$$y = \log \frac{1 - d}{d} + \log\left\{1 - \frac{(1 + d)[L]_{1-d}}{(1 - d)[L]_{1+d}}\right\} \quad . \quad . \quad . \quad . \quad (14)$$

which is useful in the absence of Fig. 1 if only occasional use is made of the correction-term, at d values which are not tabulated.*

Since the above treatment postulates the symmetry of the formation curve about its mid-point, it cannot be used for complex systems where $N > 2$. Lack of symmetry may, however, also appear even in some systems where $N = 2$ if polydentate ligands are involved. In the system Cu^{++} and diethylenetriamine (" dien "), $\bar{n}$ increases slowly with [L] over the range $1 < \bar{n} < 2$ and does not approach 2 asymptotically (Jonassen *et al., loc. cit.*). This is explicable if the second ligand molecule is not co-ordinated through each of its nitrogen

* We are grateful to one of the Referees who pointed this out, and who also made fruitful suggestions which have been incorporated in this paper.

atoms. Ligands such as αβ-diamino-carboxylate ions could chelate with metal ions in three different ways (Albert, *Biochem. J.*, 1952, **50**, 690) to give three different 1 : 1 complexes and six different 1 : 2 complexes. In these circumstances the formation curve would not be represented by equation (2). Unsymmetrical formation curves may also result if polynuclear complexes are involved. Many unsymmetrical formation curves are, however, depicted in the literature for systems where $N = 2$ and where none of these possible complications is expected. In such cases the experimental work must be regarded as suspect. It is always advisable to test an experimentally determined formation curve for symmetry about its mid-point, for, if this test fails, only limited confidence can be placed on stability constants calculated from it by any of the methods described in this paper, since they all postulate that the results may be represented accurately by equation (2).

Method H. Least-squares Treatment.—Equation (2) can be rewritten as

$$\frac{\bar{n}}{(\bar{n}-1)[\mathrm{L}]} = \frac{(2-\bar{n})[\mathrm{L}]}{(\bar{n}-1)} . K_1K_2 - K_1 \quad . \quad . \quad . \quad . \quad . \quad (15)$$

which is the equation to a straight line. Since, in practice, the term [L] may vary by several powers of ten, it is seldom convenient to plot $\bar{n}/(\bar{n}-1)[\mathrm{L}]$ against $(2-\bar{n})[\mathrm{L}]/(\bar{n}-1)$ to obtain the slope, K_1K_2, and the intercept, $-K_1$, of the best straight line. The constants are best evaluated by the method of "least squares" which makes use of all the experimental data and avoids subjective "smoothing" of data incidental to plotting the "best straight line." A minor disadvantage arises from the properties of the functions $\bar{n}/(\bar{n}-1)$ and $(2-\bar{n})/(\bar{n}-1)$, which becomes very large in the centre of the curve ($0{\cdot}95 < \bar{n} < 1{\cdot}05$) and very sensitive to slight experimental errors in $\bar{n}$. Points in this small region are therefore best rejected in this treatment.

This method was first tested on three systems with widely different values of K_1/K_2 and as many experimental points as possible. The values of K_1 and K_2 obtained by Method H being used, values of $\bar{n}$ corresponding to the experimental values of pL were calculated. Values of pL, $\bar{n}_{\mathrm{expt.}}$, and $\Delta\bar{n}(= \bar{n}_{\mathrm{expt.}} - \bar{n}_{\mathrm{calc.}})$ are given in Tables 3, 4, and 5, together with

TABLE 3. Cu^{++} *and dimethylethylenediamine ("dimen"), in water, at* 25° ($K_1/K_2 \sim 10^3$) (Irving and Griffiths, *J.*, 1953, in the press).

pL ...	10·889	10·351	10·074	9·954	9·835	9·726	9·607	9·518	9·270	8·942	8·414	7·727
$\bar{n}_{\mathrm{expt.}}$	0·048	0·192	0·313	0·374	0·433	0·493	0·553	0·614	0·773	0·853	0·971	1·088
$\Delta\bar{n}$ ...	+0·011	−0·013	−0·021	−0·021	−0·016	−0·014	−0·005	−0·016	−0·046	+0·001	−0·002	−0·007
pL ...	7·311	7·163	7·025	6·907	6·799	6·701	6·593	6·486	6·271	6·009	5·672	
$\bar{n}_{\mathrm{expt.}}$	1·202	1·259	1·319	1·376	1·432	1·491	1·547	1·604	1·716	1·821	1·918	
$\Delta\bar{n}$ ...	−0·004	+0·015	+0·004	+0·029	+0·013	+0·011	+0·017	+0·020	+0·013	+0·012	−0·003	

	$\log K_1$	$\log K_2$	$\log \beta_2$	σ
Method A	9·69	6·65	16·34	—
Method G	9·69	6·69	16·38	—
Method H	9·69	6·71	16·40	±0·017

TABLE 4. Cu^{++} *and glycine in water at* 25° ($K_1/K_2 \sim 10^{1\cdot4}$) (Irving and Griffiths, unpublished).

pL	9·612	8·667	8·607	8·549	8·492	8·423	8·358	8·294	8·221	8·150
$\bar{n}_{\mathrm{expt.}}$	0·008	0·250	0·270	0·296	0·326	0·351	0·385	0·426	0·463	0·511
$\Delta\bar{n}$	−0·005	−0·025	−0·019	−0·018	−0·019	−0·009	−0·005	−0·008	+0·001	0·000
pL	8·076	7·993	7·902	7·803	7·715	7·630	7·530	7·423	7·318	7·215
$\bar{n}_{\mathrm{expt.}}$	0·564	0·620	0·681	0·749	0·807	0·872	0·938	1·012	1·088	1·169
$\Delta\bar{n}$	−0·003	−0·002	0·000	+0·001	+0·005	−0·001	+0·001	0·000	−0·004	−0·014
pL	7·084	6·975	6·838	6·708	6·565	6·380	6·192	5·886	5·034	
$\bar{n}_{\mathrm{expt.}}$	1·251	1·339	1·425	1·515	1·606	1·697	1·788	1·880	1·972	
$\Delta\bar{n}$	−0·005	−0·016	−0·007	−0·009	−0·015	+0·002	−0·013	+0·002	+0·010	

	$\log K_1$	$\log K_2$	$\log \beta_2$	σ
Method A	8·16	6·73	14·89	—
Method G	8·13	6·78	14·91	—
Method H	8·12	6·77	14·89	±0·010

TABLE 5. Ag^+ *and ammonia in* 2N-*aqueous ammonium nitrate at* 30° ($K_1/K_2 \sim 10^{0.6}$) (Bjerrum, *loc. cit.*, p. 132).

pL	4·051	3·816	3·656	3·523	3·385	3·232	3·030
$\bar{n}_{expt.}$	0·247	0·495	0·741	0·988	1·230	1·477	1·711
$\Delta\bar{n}$	+0·002	−0·003	−0·002	+0·002	−0·004	−0·002	−0·006

	log K_1	log K_2	log β_2	σ
Method A	3·20	3·83	7·03	± 0·004
Method G	3·18	3·84	7·02	—
Method H	3·19	3·84	7·03	± 0·004

the standard deviation, $\sigma = [\Sigma(\Delta\bar{n})^2/\text{number of observations}]^{\frac{1}{2}}$. The stability constants calculated by Methods G and H are compared with those obtained by the original workers. In these three systems, it is seen that the stability constants calculated by using Method H are in very good agreement with those obtained by the original workers using Method A, and that the standard deviations of $\Delta\bar{n}$ are low. As a further test of Method H, stability constants were calculated for some systems where the workers' own method of calculation seemed suspect, or where the experimental formation curve was incomplete. The results are given in Tables 6—9.

TABLE 6. Cd^{++} *and* L-*asparagine in water* ($K_1/K_2 \sim 10^{0.6}$) (Albert, *Biochem. J.*, 1950, **47**, 531).

pL	4·75	4·40	4·10	3·80	3·62	3·45	3·30	3·16	3·05	2·92
$\bar{n}_{expt.}$	0·10	0·20	0·40	0·57	0·74	0·93	1·11	1·26	1·42	1·56
$\Delta\bar{n}$ (Albert)	+0·019	+0·040	+0·008	+0·033	+0·041	+0·012	−0·033	−0·057	−0·121	−0·152
$\Delta\bar{n}$ (Method H)	−0·014	−0·017	−0·067	−0·003	−0·003	+0·006	−0·007	+0·002	−0·051	−0·067

	log K_1	log K_2	log β_2	σ
Albert	3·87	2·90	6·77	±0·069
Method H	3·71	3·07	6·78	±0·036

The stability constants obtained by using Method H lead to much lower standard deviations of $\Delta\bar{n}$ than do those obtained by Albert, using Method D, which should only be used for systems in which $K_1/K_2 > 10^4$.

The magnitude of σ is a measure of the precision, rather than of the accuracy, of the experimental data. It is seen that the values of $\Delta\bar{n}$ obtained by using Method H are very small in the centre of the curve, but increase as d increases. This effect, which is observed with several of the systems studied, is due to the "weighting" of the central terms by the least-squares treatment. It is fortunate that the points where d is small may be determined with greater experimental precision than those where $d \longrightarrow 1$.

TABLE 7. Ni^{++} *and oxine, in* 70% *aqueous dioxan at* 25° ($K_1/K_2 \sim 10^{1.2}$) (Maley and Mellor, *Australian J. Sci. Res.*, 1949, **2**, 98).

pL	11·71	11·68	11·63	11·56	11·54	11·27	11·08
$\bar{n}_{expt.}$	0·37	0·47	0·53	0·63	0·70	0·85	1·04
$\Delta\bar{n}$ (M. and M.)	+0·128	+0·046	+0·020	−0·030	−0·084	−0·043	−0·061
$\Delta\bar{n}$ (Method H)	+0·131	+0·052	+0·014	−0·020	−0·075	−0·017	−0·021
pL	10·83	10·51	10·33	10·28	9·94	9·57	
$\bar{n}_{expt.}$	1·20	1·42	1·48	1·53	1·80	1·91	
$\Delta\bar{n}$ (M. and M.)	−0·079	−0·070	−0·003	−0·019	−0·095	−0·055	
$\Delta\bar{n}$ (Method H.)	−0·021	+0·004	+0·080	+0·033	−0·035	−0·022	

	log K_1	log K_2	log β_2	σ
Maley and Mellor	11·65	10·35	22·00	±0·068
Method H	11·64	10·47	22·11	±0·056

In this system the experimental points do not lie on a smooth curve, and even with Method H, a high value of $\sigma = \pm 0{\cdot}056$, is obtained, indicating a low precision of the data. The constants calculated by using Method H do, however, fit the experimental curve appreciably better than do these obtained by Maley and Mellor, using Method C. It has been pointed out (p. 3400) that the use of Method C is not justified unless $K_1/K_2 > 10^{2{\cdot}5}$.

Values of $\bar{n}$ ($= 1 \pm d$) are only recorded in the two regions where $d \cong 0{\cdot}5$, but it is seen that, even with such a very incomplete formation curve, Method H gives satisfactory

results, which are in good agreement with those obtained by Jonassen *et al.*, using, in effect, Method C. This would be expected in such a system, where $K_1/K_2 > 10^{2.5}$.

This system is also represented by an incomplete formation curve ($0.85 < \bar{n} < 1.75$). Johnston and Freiser used Method C to obtain K_2, but do not indicate how K_1 was calculated. From the value they obtained, it seems possible that equation (9) was used. This illustrates the misleading results which may be obtained when Method C is applied to a formation curve where $K_1 \cong K_2$. Values of $\bar{n}$ calculated from stability constants given by the authors differ considerably from the experimental values. Not only are the deviations large, but there is an unmistakable trend in their magnitude. On recalculation by Method H, a

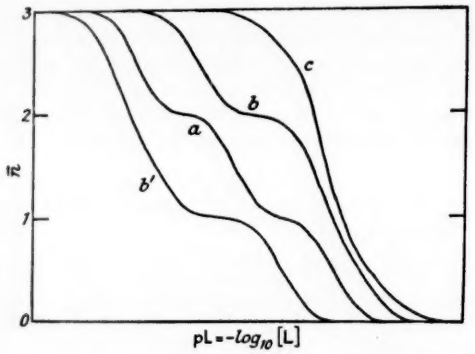


FIG. 2. *Formation curves.*

satisfactory fit is obtained with $\log K_1 = 13.05$ and $\log K_2 = 13.15$, values which differ considerably in magnitude from those calculated by the authors, who, moreover, report $\log K_1 > \log K_2$. It is significant that the revised value for the overall constant β_2 is in good agreement with that previously obtained; this emphasises that calculated values of K_1 and K_2 may together satisfy equation (9), although the individual constants may both be in error.

TABLE 8. Ni^{++} *and "dien," in water at* 30° ($K_1/K_2 \sim 10^{2.7}$) (Jonassen *et al., loc. cit.*).

pL	11·10	11·05	10·97	10·68	10·51	10·39
$\bar{n}_{expt.}$	0·376	0·406	0·443	0·582	0·639	0·689
$\Delta\bar{n}$ (Jonassen)	−0·015	−0·018	−0·011	+0·016	+0·051	+0·055
$\Delta\bar{n}$ (Method H)	−0·023	−0·033	−0·025	+0·002	+0·038	+0·047
pL	8·55	8·32	8·16	8·09	7·93	7·78
$\bar{n}_{expt.}$	1·295	1·399	1·502	1·532	1·604	1·679
$\Delta\bar{n}$ (Jonassen)	−0·019	−0·003	−0·015	−0·004	+0·014	+0·015
$\Delta\bar{n}$ (Method H)	−0·019	−0·003	−0·014	−0·004	+0·015	+0·018

	$\log K_1$	$\log K_2$	$\log \beta_2$	σ
Jonassen *et al.*	10·85	8·14	18·99	±0·025
Method H	10·82	8·14	18·96	±0·024

TABLE 9. Cu^{++} *and oxine in* 50% *aqueous dioxan* ($K_1/K_2 \sim 1$) (Johnston and Freiser, *J. Amer. Chem. Soc.*, 1952, **74**, 5340).

pL	13·18	13·16	13·07	13·05	12·89	12·74	12·72	12·50
$\bar{n}_{expt.}$	0·84	0·90	1·05	1·11	1·33	1·48	1·55	1·75
$\Delta\bar{n}$ (J. and F.)	+0·087	+0·048	−0·037	−0·048	−0·103	−0·109	−0·16	−0·180
$\Delta\bar{n}$ (Method H)	+0·035	+0·008	0·000	−0·014	+0·035	−0·013	−0·020	−0·018

	$\log K_1$	$\log K_2$	$\log \beta_2$	σ
Johnston and Freiser	13·49 (calc.)	12·73	26·22	±0·108
Method H	13·05	13·15	26·20	±0·021

In view of the real possibilities of authors' failing to obtain the most satisfactory constants from their experimental data through unsatisfactory methods of computation, it is clearly desirable to state precisely the method of calculation adopted, so that even in the absence of experimental values for $\bar{n}$ and pL it would be possible to assess the reliability

of the values given and even to estimate with the aid of Fig. 1 or Table 2 the order of magnitude of the correction which must be applied.

Systems of Higher Complexity.—There are no simple methods of calculating stability constants in systems where $N \geqslant 3$. If all the successive constants differ greatly in magnitude the formation curve has N distinct steps (cf. Fig. 2*a* for the case where $N = 3$) and Method C can be used. When $N = 3$ and $K_1 \sim K_2 \gg K_3$, the formation curve will show only two steps, corresponding to $0 < \bar{n} < 2$, and $2 < \bar{n} < 3$ (Fig. 2*b*). Here $\log K_3 = \mathrm{pL}_{2\frac{1}{2}}$ (Method C) and K_1 and K_2 may be calculated by treating the lower step as a complete formation curve of a system where $N = 2$, using one of the appropriate methods described above. Fig. 2*b* represents a formation curve where $K_1 \gg K_2 \cong K_3$, which can again be treated as if it consisted of two separate portions. When the successive complexes are of similar stability the curve loses its wave-like character (Fig. 2*c*) and a set of trial constants [obtained appropriately from equation (5)] must be refined by successive approximation by using the following equation

$$\log K_{\bar{n}} = \mathrm{pL}_{\bar{n}} + \log\left\{ \sum_{t=0}^{t=n-1} (\bar{n} - t)\beta_t [\mathrm{L}]^t \Big/ \sum_{t=n}^{t=N} \frac{(t - \bar{n})\beta_t [\mathrm{L}]^{t-1}}{K_n} \right\} \quad . \quad (16)$$

The general equation (1) for a formation curve may be written in the form

$$\sum_{n=0}^{n=N} \frac{(\bar{n} - n)}{(\bar{n} - 1)} \cdot [\mathrm{L}]^{n-1} \beta_n = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

of which equation (15) is a particular case for $N = 2$. If there are m experimental values for the points ($\bar{n}$, pL), substitution in (17) will give m inhomogeneous linear equations in $\beta_1, \beta_2 \ldots \beta_N$. The normal equations obtained therefrom by the usual methods form a set of N simultaneous linear equations which can be solved for $\beta_1, \beta_2 \ldots \beta_N$ by matrix or other methods.

Grateful acknowledgment is made to the Ministry of Supply for a grant to one of us (H. S. R.).

Inorganic Chemistry Laboratory,
South Parks Road, Oxford.

[*Received, November 8th,* 1952.]

---

681. *Some Photochemical Reactions between Quinones and Hydrocarbons.*

By R. F. Moore and William A. Waters.

The photochemical dehydrogenations of *p*-xylene, cumene, and tetralin by means of phenanthraquinone, chloranil, and 1 : 4-naphthaquinone have been examined. A study of the reaction products shows that the hydrogen abstraction is homolytic.

In a previous paper (*J.*, 1953, 238) we suggested that the photochemical addition of benzaldehyde to the oxygen atoms of phenanthraquinone was a chain reaction promoted by the activation of the quinone to a diradical which was capable of abstracting a hydrogen atom from the aldehyde molecule. Since it had previously been suggested (Waters, *Ann. Reports*, 1945, **42**, 155; *Trans. Faraday Soc.*, 1946, **42**, 184; Dost and Van Nes, *Rec. Trav. chim.*, 1951, **70**, 403; 1952, **71**, 857) that the high-temperature thermal dehydrogenations of hydroaromatic substances by means of quinones involve a similar hydrogen-atom transfer, $\mathrm{Q} + \mathrm{H{-}R} \longrightarrow \mathrm{H{-}Q}\cdot + \cdot\mathrm{R}$, we decided to obtain further support for this reaction mechanism by investigating corresponding photochemical reactions at room temperature.

Benrath and von Meyer (*J. prakt. Chem.*, 1914, **89**, 258) had previously shown that phenanthraquinone reacted with *o*- and *p*-xylenes, and with *ψ*-cumene, on prolonged exposure to sunlight to give their phenanthrenediol monoethers, structurally similar to the phenanthrenediol monobenzoate discussed in our previous paper (*loc. cit.*). From corresponding reactions with *m*-xylene, mesitylene, and *p*-cymene however they isolated only phenanthraquinhydrone and did not discover the natures of the products derived from the hydrocarbons. Schönberg and Mustapha (*J.*, 1944, **67**; 1945, **657**) observed

the production of tetra-arylethanes from diarylmethanes on irradiation in sunlight with *p*-benzoquinone, phenanthraquinone, and anthraquinone, but obtained no evidence of addition of diarylmethyl radicals to quinone molecules.

We have now examined the reactions which occur when solutions of phenanthraquinone, chloranil, and 1 : 4-naphthaquinone in *p*-xylene, cumene, and tetralin are exposed, in the absence of air, to the radiation from a 500-w Hanovia mercury-in-quartz lamp and have been able to identify each of the reaction products which are tabulated below.

Products of photochemical dehydrogenations of hydrocarbons.

Hydrocarbon	Phenanthraquinone	Chloranil	1 : 4-Naphthaquinone
p-Xylene	9-Hydroxy-10-*p*-methylbenzyloxyphenanthrene, 33% 1 : 2-Di-*p*-tolylethane, 2%	Tetrachloroquinol, 6% 2 : 3 : 5 : 6-Tetrachloro-4-*p*-methylbenzyloxyphenol, 90% Hydrogen chloride	1 : 4-Dihydroxynaphthalene, 65% 1 : 2-Di-*p*-tolylethane, 8%
Cumene	Phenanthraquinhydrone, 85% α-Methylstyrene 2 : 3-Dimethyl-2 : 3-diphenylbutane, 3%	Tetrachloroquinol, 63% α-Methylstyrene Hydrogen chloride	1 : 4-Dihydroxynaphthalene, 40% α-Methylstyrene
Tetralin	Phenanthraquinhydrone, 18% 1 : 2-Dihydronaphthalene, 50%	Tetrachloroquinol, 55% 1 : 2-Dihydronaphthalene, 21%	1 : 4-Dihydroxynaphthalene, 52% 1 : 2-Dihydronaphthalene, 10%

From the reaction of *p*-xylene with *p*-benzoquinone only quinhydrone could be isolated.

As can be said of the results of Schönberg and Mustapha, the isolation of hydrocarbon dimers, R–R ($Me{\cdot}C_6H_4{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_4{\cdot}Me$ and $Ph{\cdot}CMe_2{\cdot}CMe_2Ph$) gives clear evidence that free hydrocarbon radicals, R·, must have been formed from both *p*-xylene and cumene, and so substantiates the homolytic mechanism for quinone dehydrogenation. Correspondingly phenanthraquinhydrone and quinhydrone can be regarded as the dimers of the semiquinone radicals HQ·. It may be noted that only from the reactions involving *p*-xylene was it possible to isolate any combination products of the unlike radicals R· and HQ·. Whereas the *p*-methylbenzyl radical, $Me{\cdot}C_6H_4{\cdot}CH_2{\cdot}$, which cannot easily yield a stable olefin by the loss of a hydrogen atom, does preponderatingly form the cross combination product, R·QH, with semiquinone radicals, both the αα-dimethylbenzyl and the α-tetralyl radical seem to react by hydrogen loss rather than by addition, *e.g.*

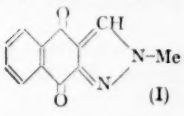
$$Ph{\cdot}CMe_2{\cdot} + {\cdot}Q{-}H \longrightarrow Ph{\cdot}CMe{:}CH_2 + H{-}Q{-}H.$$

However Criegee (*Ber.*, 1936, **69**, 2758), who obtained quinol monoethers by warming *cyclo*hexene and tetralin with dichloroquinizarinquinone, found that the addition products were unstable at high temperatures and similarly yielded mixtures of olefins and quinols (cf. Ziegler and Deparade, *Annalen*, 1950, **567**, 128), but it can be doubted whether this thermal decomposition would occur so readily under our reaction conditions. Since quinol monoethers were not formed extensively except from the reaction between *p*-xylene and chloranil it is unlikely that these photochemical dehydrogenations involve long reaction chains of the type, $R{\cdot} + Q \longrightarrow R{-}Q : R{-}Q{\cdot} + H{-}R \longrightarrow R{-}Q{-}H + {\cdot}R$, postulated for the much easier photochemical reactions between aldehydes and quinones.

The formation of some hydrogen chloride from the reactions involving chloranil apparently indicates that some of the photochemically produced radicals must be active enough to attack nuclear chlorine.

It may be noted that the infra-red spectrum of 9-hydroxy-10-*p*-methylbenzyloxyphenanthrene shows absorption bands indicative of both H–O and C=O bonds, in confirmation of the keto–enol tautomerism suggested for it by Benrath and von Meyer (*loc. cit.*). Our failure to effect any reaction of it with diazomethane indicates that the ketonic form predominates. In contrast, the corresponding *p*-methylbenzyl ether of tetrachloroquinol exhibits no ketonic properties.

Attention may also be directed to the fact that the methylation of 1 : 4-dihydroxynaphthalene with an ethereal solution of diazomethane yields 1-methylnaphthaquinono-(2′ : 3′-3 : 4)pyrazole (I). This is also obtained by the action of diazomethane on the naphthaquinono(2′ : 3′-3 : 4)pyrazole itself, though Fieser and Peters (*J. Amer. Chem. Soc.*, 1931, **53**, 4081) found that methylation with methyl sulphate produced the isomeric α-methyl derivative (cf. Auwers and Düesberg, *Ber.*, 1920, **53**, 1179).



(I)

Experimental

The photochemical reactions were carried out by shaking the reactants mechanically in thin-walled soft-glass bulbs, sealed under nitrogen, in the radiation from a 500-w mercury-in-quartz Hanovia lamp placed about 25 cm. away.

Irradiations with Cumene.—Commercial cumene was purified by shaking it with portions of 98% sulphuric acid until the acid layer was not discoloured, washing it with water, dilute sodium carbonate and water again, drying ($CaCl_2$) and fractionating it. The distillate, b. p. 149—152°, was then hydrogenated for 2 hr. at 80°/60 atm., Raney nickel being used. The product on refractionation gave 95% of material, b. p. 151—152°.

(a) *With phenanthraquinone.* The quinone (2 g.) in cumene (35 ml.) was irradiated for 20 days. The blackish phenanthraquinhydrone (1·7 g.; m. p. 165—169°) which separated gave a green colour with alkali and phenanthraquinone when boiled with alcohol. Reductive acetylation with zinc dust and acetic anhydride gave 9 : 10-diacetoxyphenanthrene, m. p. and mixed m. p. 202°. After evaporation of excess of cumene, the residue was chromatographed on alumina. The first eluates, ligroin being used, yielded 2 : 3-dimethyl-2 : 3-diphenylbutane (0·1 g.), needles (from ethanol), m. p. 118—119° which was unchanged after admixture with an authentic specimen (Kharasch and Urry, *J. Org. Chem.*, 1948, **13**, 108) (Found: C, 90·3; H, 9·0. Calc. for $C_{18}H_{22}$: C, 90·8; H, 9·2%).

The presence of α-methylstyrene was established by Tiffeneau's method (*Ann. Chim. Phys.*, 1907, **10**, 165). The cumene distillate (25 ml.) was stirred vigorously for 2 hr. with 1% aqueous neutral potassium permanganate (200 ml.) at 0°. The solution was decolorised (SO_2) and extracted with ether, and the dried extract was fractionated. The final 3 ml. when warmed with dinitrophenylhydrazine in aqueous alcohol yielded acetophenone dinitrophenylhydrazone, m. p. an mixed m. p. 237°. The purified cumene used for the irradiation gave no similar reaction.

(b) *With chloranil.* The quinone (2 g.) in cumene (35 ml.) was irradiated for 30 days. When the bulb was broken hydrogen chloride escaped. The solid which had separated (1·3 g.) proved to be tetrachloroquinol (m. p. and mixed m. p. 236°; dibenzoate, m. p. and mixed m. p. 238°). After evaporation of the cumene the small residue (0·5 g.) was fractionated through alumina but gave no pure products. Permanganate oxidation, as above, of the cumene distillate established the presence of α-methylstyrene.

The hydrogen chloride formed in another experiment was estimated after absorption in water. The amount corresponded to the abstraction of one chlorine atom from about 25% of the chloranil.

(c) *With 1 : 4-naphthaquinone.* The quinone (2 g.) in cumene (35 ml.) was irradiated for 21 days. The blackish solid which separated (0·85 g.), when rubbed with benzene gave 1 : 4-dihydroxynaphthalene (0·5 g.; needles, m. p. and mixed m. p. 191°, from toluene; dibenzoate, m. p. and mixed m. p. 169°). The filtrate on evaporation gave naphthaquinhydrone (0·1 g.) which on reductive acetylation yielded 1 : 4-diacetoxynaphthalene, m. p. 128°. Permanganate oxidation of the cumene established the presence of α-methylstyrene.

Irradiations with Tetralin.—The tetralin, which had been fractionated through a 50-plate column (by Imperial Chemicals Limited, Billingham), was shaken with 98% sulphuric acid, sodium hydrogen carbonate solution, and water, and then refractionated over sodium: it had b. p. 206°.

(a) *With phenanthraquinone.* The quinone (2 g.) in tetralin (50 ml.) was irradiated for 18 days. Phenanthraquinhydrone separated (0·35 g.) and was identified as above. Evaporation of the tetralin left an amorphous residue. Bromination of the distillate with 10% solution of bromine in chloroform at 0° until the colour no longer faded rapidly (about 0·4 ml. of bromine required) and subsequent removal of solvents yielded 1 : 2-dibromo-1 : 2 : 3 : 4-tetrahydronaphthalene (0·7 g.; m. p. and mixed m. p. 71° after crystallisation from ligroin) (Found: Br, 55·1. Calc. for $C_{10}H_{10}Br_2$: Br, 55·2%).

(b) *With chloranil.* The quinone (2 g.) in tetralin (50 ml.) was irradiated for 39 days. When the bulb was broken hydrogen chloride escaped. Separated tetrachloroquinol (1 g.) was identified as above and more (0·15 g.) was obtained by evaporation of the solvent. On bromination this distillate gave dibromotetralin (0·5 g.).

(c) *With* 1 : 4-*naphthaquinone.* The quinone (2 g.) in tetralin (30 ml.) was irradiated for 21 days. Dihydroxynaphthalene (1·05 g.) separated and was identified as above. The filtrate on evaporation and bromination gave dibromotetralin (0·3 g.).

Irradiations with p-*Xylene.*—(a) *With phenanthraquinone* (*compare Benrath and von Meyer*, loc. cit.). The quinone (2 g.) in *p*-xylene (30 ml.) was irradiated for 18 days. After evaporation of the solvent, the residue was chromatographed on alumina. Ligroin eluted 1 : 2-di-*p*-tolylethane (0·2 g.), plates, m. p. 81°, from aqueous ethanol (Found : C, 90·9; H, 8·7. Calc. for $C_{16}H_{18}$: C, 91·4; H, 8·6%). The m. p. was not depressed by admixture with an authentic specimen prepared by persulphate oxidation of *p*-xylene (Moritz and Wolffenstein, *Ber.*, 1899, **32**, 433, 2531). Chloroform eluted a gum which when rubbed with alcohol gave 9-hydroxy-10-*p*-methylbenzyloxyphenanthrene (1 g.). This crystallised from alcohol or ligroin in pale yellow prisms, m. p. 128—129° (Found : C, 84·0; H, 5·7. Calc. for $C_{22}H_{18}O_2$: C, 84·1; H, 5·7%), and its infra-red spectrum showed characteristic bands at 2·88 μ for H—O stretching and at 5·96 μ for conjugated C=O stretching. The compound failed to react with an ethereal solution of diazomethane.

(b) *With chloranil.* The quinone (2 g.) in *p*-xylene (25 ml.) was irradiated for 40 days. When the bulb was broken hydrogen chloride escaped. The separated solid (0·12 g.) crystallised from acetic acid in needles, m. p. 236° undepressed by admixture with tetrachloroquinol. Evaporation of the *p*-xylene and treatment of the residue with ligroin gave 2 : 3 : 5 : 6-*tetrachloro*-4-p-*methylbenzyloxyphenol* (1·8 g.) which crystallised from acetic acid in needles, m. p. 125° (Found : C, 47·7; H, 2·8; Cl, 39·7. $C_{14}H_{10}O_2Cl_4$ requires C, 47·7; H, 2·8; Cl, 40·3%). It was soluble in cold alkali, gave no colour with alcoholic ferric chloride and no reaction with dinitrophenylhydrazine. The infra-red spectrum showed the characteristic H—O stretching band at 2·94 μ but no carbonyl band. The *acetate* crystallised from aqueous alcohol in needles, m. p. 106° (Found : C, 48·5; H, 3·1; Cl, 36·3. $C_{16}H_{12}O_3Cl_4$ requires C, 48·7; H, 3·1; Cl, 36·0%). Methylation of the monoether (0·4 g.) at 0° for 24 hr. with diazomethane (from 1 g. of nitrosomethylurea) gave 2 : 3 : 5 : 6-*tetrachloro*-4-p-*methylbenzyloxyphenylmethyl ether*, needles, m. p. 153° (from ethanol) (Found : C, 49·9; H, 3·2; Cl, 38·3. $C_{15}H_{12}O_2Cl_4$ requires C, 49·2; H, 3·3; Cl, 38·8%).

(c) *With* 1 : 4-*naphthaquinone.* The quinone (2 g.) in *p*-xylene (30 ml.) was irradiated for 16 days. 1 : 4-Dihydroxynaphthalene (1·2 g.) separated and was identified as above. After evaporation of the solvent the residue was methylated with diazomethane, and the product was fractionated on alumina. Ligroin eluted 1 : 2-di-*p*-tolylethane (0·05 g.), m. p. 81°, and following this chloroform eluted a gum which when rubbed with alcohol gave 1-*methylnaphthaquinono*(2′ : 3′-3 : 4)*pyrazole* (0·1 g.), small needles, m. p. 176°, from alcohol (Found : C, 68·0; H, 3·8; N, 13·2. $C_{12}H_8O_2N_2$ requires C, 67·9; H, 3·8; N, 13·2%). Its infra-red spectrum showed the characteristic band at 5·95 μ indicative of conjugated C=O, but no band indicative of N—H. The compound was insoluble in alkali. It was also obtained (i) by the action of diazomethane (from 4 g. of nitrosomethylurea) on 1 : 4-dihydroxynaphthalene (0·5 g.) in ether at 0° (yield 0·35 g.), and (ii) by the action of diazomethane on naphthaquinono-(2′ : 3′-3 : 4)-pyrazole (Fieser and Peters, *loc. cit.*) in dioxan–ether solution.

(d) *With* p-*benzoquinone.* The quinone (2 g.) in *p*-xylene (30 ml.) was irradiated for 9 days. Quinhydrone (1·1 g.) separated as a black solid which on reductive acetylation gave quinol diacetate, m. p. and mixed m. p. 122°. After evaporation of the *p*-xylene the residue gave no crystalline products.

This work has been carried out on behalf of the D.S.I.R. Road Tar Research Committee.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, June 12th*, 1953.]

682. *The Reactions of Hexachlorodisilane with Ammonium Halides and Trimethylamine Hydrohalides.*

By C. J. Wilkins.

A somewhat complex reaction occurs between hexachlorodisilane and ammonium halides, leading to the formation, for example, of silicon tetrachloride and trichlorosilane in approximately equimolecular proportions and silicon–nitrogen condensation products of low volatility. The evidence indicates initiation by ammonia from thermal decomposition of the ammonium halide, and ammonia itself brings about a similar reaction. Trimethylamine hydrochloride decomposes hexachlorodisilane catalytically according to the equation $n Si_2Cl_6 \longrightarrow (SiCl_2)_n + n SiCl_4$, this reaction likewise being initiated by the free base.

The corresponding decompositions of ethylpentachlorodisilane and diethyltetrachlorodisilane with ammonium chloride and trimethylamine hydrochloride have also been examined. The behaviour of samples of the diethyl derivative gave information about the isomeric composition of this material as obtained from the interaction of ethylmagnesium bromide and hexachlorodisilane.

In an attempt to fluorinate hexachlorodisilane with ammonium fluoride it was found that the ammonium salt did not effect a simple halogen exchange (compare Wilkins, *J.*, 1951, 2726) but caused cleavage of the Si–Si bond, giving trichlorosilane, trichlorofluorosilane, and silicon tetrachloride as the chief volatile products. This type of reaction also extends to the other ammonium halides, and from the disilane and ammonium halide, in each case trichlorosilane and the tetrachloride were recovered in approximately equimolecular proportions (see Table). The formation of trichlorosilane and silicon tetrachloride from the reaction with ammonium chloride, for example, may *in effect* be represented: $Si_2Cl_6 + HCl \longrightarrow SiHCl_3 + SiCl_4$, but these volatile products account for only about 60% of the silicon, the rest remaining in the involatile residue which contains silicon–nitrogen condensation products. Ammonium bromide and ammonium iodide also yield trichlorosilane and silicon tetrachloride with no trace of bromide or iodide in the volatile products.

The degradation of an unsymmetrical derivative of hexachlorodisilane is illustrated by the reaction of ammonium chloride with ethylpentachlorodisilane. The volatile products (see Table) are ethyltrichlorosilane and trichlorosilane, but no ethyldichlorosilane or silicon tetrachloride, so that the reaction is to be represented as following course (1) rather than (2).

$$EtSiCl_2{\cdot}SiCl_3 \xrightarrow{NH_4Cl} EtSiCl_3 + SiHCl_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$EtSiCl_2{\cdot}SiCl_3 \xrightarrow{NH_4Cl} EtSiHCl_2 + SiCl_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Further, in an application of the ammonium chloride reaction, described below, for determining the isomeric composition of a sample of diethyltetrachlorodisilane, diethyldichlorosilane and trichlorosilane, but no diethylchlorosilane or silcon tetrachloride, were found among the products. It was therefore inferred that the unsymmetrical isomer had reacted analogously to the monoethyl derivative according to (3) and not (4).

$$Et_2SiCl{\cdot}SiCl_3 \xrightarrow{NH_4Cl} Et_2SiCl_2 + SiHCl_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$Et_2SiCl{\cdot}SiCl_3 \xrightarrow{NH_4Cl} Et_2SiHCl + SiCl_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The order of reactivities of the ethyl derivatives towards ammonium chloride, $Si_2Cl_6 \approx EtSi_2Cl_5 > Et_2Si_2Cl_4 > Si_2Et_6$, is also the order in which acceptor properties will decrease. The correlation may be indirect in its significance, or even fortuitous, but encouraged the working assumption that the reaction is initiated by a nucleophilic attack on silicon, to which this atom is prone. Possible attacking reagents are chloride ion, or hydrogen chloride or ammonia from thermal decomposition of the ammonium halide.

The course of the degradation of the ethyl derivatives, however, does not suggest an initial attack by chloride ion for this would be likely to occur at the more highly charged and, probably too, more accessible silicon atom already linked to the larger number of chlorine atoms to yield products from reactions (2) and (4) rather than (1) and (3). It was found too that hydrogen chloride alone does not react with hexachlorodisilane (vapour)

Reaction of hexachlorodisilane and its ethyl derivatives with ammonium halides.

Reactants	Time, hr.	Temp.	Yields, %, of $SiHCl_3$	$SiFCl_3$	$SiCl_4$	
$Si_2Cl_6 + NH_4F$	60	125—130	33	22	8 *	
$Si_2Cl_6 + NH_4Cl$	36	130—140	30	—	28	
,, ...	15	145	28	—	32	
$Si_2Cl_6 + NH_4Br$	48	145	30	—	27	
$Si_2Cl_6 + NH_4I$	90	145	12	—	10 †	
			$SiHCl_3$	$EtSiCl_3$	Et_2SiCl_2	$EtSiHCl_2$
$EtSi_2Cl_5 + NH_4Cl$	15	160	33	28	—	—
$Et_2Si_2Cl_4 + NH_4Cl$	72	200	5	19	5	16
$Si_2Et_6 + NH_4Cl$	—	250	No reaction			
$Si_2Et_6 + NH_4F$	—	200	Si_2Et_6 recovered			

* Also a mixture of more volatile fluorinated products. † Reaction was incomplete.

in a silica tube below 550°, or below 400° in the presence of potassium chloride. On the other hand direct evidence for ammonia as initiating reagent was obtained. Addition of ammonia to hexachlorodisilane causes the separation of solid, but a subsequent reaction which occurs at 60—70° gives trichlorosilane and silicon tetrachloride in yields comparable with those obtained by the use of ammonium chloride. There is no possibility that this reaction with ammonia takes place through intermediate formation of ammonium chloride since the ammonium chloride reaction does not appear below 120—130°.

The formation of silicon–nitrogen condensation products cannot occur when trimethylamine or its hydrohalides are used in place of ammonia or ammonium salts. These reagents (apart from the hydrofluoride which was not examined) bring about, instead, a catalytic decomposition of hexachlorodisilane according to the ideal equation

$$n\mathrm{Si_2Cl_6} \longrightarrow (\mathrm{SiCl_2})_n + n\mathrm{SiCl_4} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The yield of silicon tetrachloride is almost quantitative and samples of the involatile polymer were of composition $SiCl_{2\cdot05}$—$SiCl_{2\cdot10}$. The material is thus of similar composition to the complex silicon chlorides $Si_{10}Cl_{22}$, $(SiCl_2)_n$, and $Si_{25}Cl_{52}$ (approx.) described by Schwarz and his co-workers (*Z. anorg. Chem.*, 1937, **232**, 241; 1937, **232**, 249; *Ber.*, 1947, **80**, 444).

As with ammonia and the ammonium halides, trimethylamine decomposes hexachlorodisilane at a lower temperature (room temperature) than does its hydrochloride (80°) so that the latter almost certainly reacts through thermal decomposition to the free base. The formation of trichlorosilane in the reactions with ammonium halides but not with trimethylamine hydrohalides is consistent with the view that attack by the free base is involved in both cases.

The decomposition of ethylpentachlorodisilane under the influence of trimethylamine hydrochloride gave ethyltrichlorosilane in 80—85% yield, so that essentially the reaction follows the course

$$n\mathrm{EtSiCl_2{\cdot}SiCl_3} \longrightarrow (\mathrm{SiCl_2})_n + n\mathrm{EtSiCl_3} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

No silicon tetrachloride or other volatile products could be detected. Hence the reaction steps leading to the formation of the polymer must include disruption of the Si–Si bond in all of the disilane molecules.

The Degradation of Diethyltetrachlorodisilane and Determination of its Isomeric Composition.—This compound may exist as the symmetrical $(EtSiCl_2)_2$ or the unsymmetrical isomer $Et_2SiCl{\cdot}SiCl_3$. There was no evidence from its distillation behaviour of the presence of two isomers in the substance, as obtained from the reaction between hexachlorodisilane and ethylmagnesium bromide. Degradation of the material with ammonium chloride and trimethylamine hydrochloride indicated, nevertheless, that both isomers were present. The products from the ammonium chloride reaction (see Table)

were diethyldichlorosilane and trichlorosilane in almost equimolecular amounts from reaction (3), and ethyldichlorosilane and ethyltrichlorosilane, also in an almost equimolecular ratio, from degradation of the symmetrical isomer :

$$EtSiCl_2{\cdot}EtSiCl_2 \xrightarrow{NH_4Cl} EtSiHCl_2 + EtSiCl_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The proportions in which the two pairs of degradation products were recovered corresponds to a three- or four-fold predominance of the symmetrical isomer. While this result must be treated with some reserve in view of the rather low total yield of volatile products, the behaviour of a sample of diethyltetrachlorodisilane with trimethylamine hydrochloride was in substantial accord. A small proportion of the disilane decomposed to give diethyldichlorosilane, but the remainder was resistant to decomposition either by the hydrochloride or by the free base. If the dichlorosilane arose from the decomposition of the unsymmetrical isomer :

$$n\mathrm{Et_2Si_2Cl_4} \longrightarrow (\mathrm{SiCl_2})_n + n\mathrm{Et_2SiCl_2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

analogous to equation (6), the yield corresponded to the presence of 15—25% of this isomer. The resistance of the symmetrical isomer to decomposition may be attributable to reduction in the susceptibility of *both* silicon atoms to nucleophilic attack, but this is not the only explanation possible.

The diethyltetrachlorodisilane isomers must be considered as produced by further ethylation of ethylpentachlorodisilane formed as an intermediate. Hence the presence of the isomers in the above proportions means that the probability that replacement of chlorine in the molecule $EtSi^{(i)}Cl_2{\cdot}Si^{(ii)}Cl_3$ by the use of ethylmagnesium bromide will occur at atom (ii) is about four times as great as at atom (i).

Experimental

Reagents.—Ammonium halides were dried and pulverised before use. Hexachlorodisilane of technical grade was fractionally distilled (b. p. 146—147°); some was also prepared by controlled chlorination of calcium disilicide (" Inorganic Syntheses," Vol. I, H. S. Booth, ed., McGraw-Hill, New York, p. 42).

Reactions with Ammonium Halides.—About 0·08 mole of hexachlorodisilane, or its ethyl derivatives, and an excess (0·3—0·4 mole) of ammonium salt were used in each experiment. Reactions were carried out in a 40-ml. flask fitted through ground joints with a distillation head leading to a trap at −78°. The flask was heated in an oil-bath so long as volatile products passed over. The crude condensate was fractionated through an 18-in. column of glass helices, toluene or *p*-cymene being used as " chasers." Re-distillation of small intermediate fractions was sometimes necessary to give sufficiently complete separation. Each compound distilled within 1—2° of the accepted boiling point, and the identities of the degradation products from diethyltetrachlorodisilane were confirmed by chloride analysis.

The non-volatile products comprise material which could not be pumped from the reaction vessel under the vacuum from a mechanical pump. The residue from the reaction between ammonium chloride and hexachlorodisilane was partly recovered by ether extraction as an oil in which the ratio Si : N was 1·74 : 1.

The Reaction between Ammonia and Hexachlorodisilane.—Ammonia (0·05 mole) was distilled into an ampoule containing hexachlorodisilane (0·04 mole). An exothermic reaction occurred at room temperature, and a crust of solid formed over the surface of the liquid. Further reaction, which commenced at about 60°, gave trichlorosilane (0·023 mole) and silicon tetrachloride (0·024 mole).

The Catalytic Decomposition of Hexachlorodisilane by Trimethylamine and its Hydrochloride.—These reactions were generally carried out with not more than 0·25 g. of catalyst. In a typical experiment, trimethylamine hydrochloride and hexachlorodisilane (8·5 g.) were warmed to 80—100°, giving 5·0 g. of silicon tetrachloride [theoretically obtainable from reaction (5) : 5·3 g.]. Trimethylamine reacted at ordinary temperature. Addition of 3 drops of the base to 10 g. of hexachlorodisilane at 15° caused a temperature rise of 20° accompanied by a slow separation of white solid; the residue was freed from volatile material at 100° [Found : Si, 27·0; Cl, 70·5. Calc. for $(SiCl_2)_n$: Si, 28·4; Cl, 71·6%]. The polymer dissolves very readily in dilute alkali with evolution of hydrogen; ammonia converts the material into silicic acid, again with evolution of hydrogen. It inflames in air below 100° and frequently ignites in contact with water.

The Action of Trimethylamine Hydrochloride on Diethyltetrachlorodisilane.—The disilane (14 g.) was heated with trimethylamine hydrochloride (0·25 g.), at first under reflux. A little solid quickly separated. Fractional distillation of the volatile products gave diethyldichlorosilane (1·5—2·0 g.), most of which distilled at 128—130°, and a small quantity of unidentified lower-boiling material. (*p*-Cymene was added as " chaser " since it was not expected that any sufficiently low-boiling material would remain.) By use of diphenyl as " chaser " some 9 g. of distillate were then obtained within the range 190—220°, and systematic redistillation gave about 6 g. of unchanged diethyltetrachlorodisilane, b. p. 203—209°, there being some loss of material in handling. This material was unchanged by further treatment with trimethylamine or its hydrochloride.

Preparation of Ethylpentachlorodisilane and Diethyltetrachlorodisilane.—These compounds were obtained by the interaction of hexachlorodisilane and ethylmagnesium bromide in appropriate proportions. Schumb and Saffer (*J. Amer. Chem. Soc.*, 1939, **61**, 363) have reported this reaction as suitable for the preparation of hexaethyldisilane, but its application to the preparation of intermediate products is new.

In the preparation of ethylpentachlorodisilane, a solution of ethylmagnesium bromide (from 0·13 g.-atom of Mg) was added dropwise during ½ hr. to a rapidly stirred solution of hexachlorodisilane (0·11 mole) in ether (200 ml.), cooled in ice water. After being stirred for a further ½ hr., the mixture was heated under reflux for 2 hr., filtered, and fractionally distilled. The *pentachloro*-compound (10 g.) had b. p. 182—184° (Found: by Mohr's titration, Cl, 67·1. Calc. for $EtSi_2Cl_5$: Cl, 67·5%).

Diethyltetrachlorodisilane was prepared similarly from hexachlorodisilane (0·22 mole) and ethylmagnesium bromide (from 0·50 g.-atom of Mg). The product (15 g.) had b. p. 206—209° (Found: gravimetrically, Cl, 55·7. $Et_2Si_2Cl_4$ requires Cl, 55·3%. The small fraction, b. p. 219—223°, was examined to determine whether it contained a concentration of one of the isomers. The chlorine content accorded closely, however, with that calculated for triethyltrichlorodisilane (Found: Cl, 47·9. Calc. for $Et_3Si_2Cl_3$: Cl, 48·0%). The close agreement between these values is probably fortuitous as the purity of this small fraction was not considered high.

The author gratefully acknowledges a grant from the research fund of the University of New Zealand.

CANTERBURY UNIVERSITY COLLEGE,
CHRISTCHURCH, NEW ZEALAND.

[*Received, May 26th*, 1953.]

---

683. *Homolytic Aromatic Substitution. Part IV.* Partial Rate Factors for the Phenylation of Fluorobenzene, Bromobenzene, and Iodobenzene.*

By D. R. AUGOOD, J. I. G. CADOGAN, D. H. HEY, and GARETH H. WILLIAMS.

The rates of attack relative to nitrobenzene by phenyl radicals (generated from benzoyl peroxide) on fluorobenzene, bromobenzene, and iodobenzene have been measured, and from these measurements the rates of attack on these compounds relative to benzene have been calculated. The ratios of the *ortho*-, *meta*-, and *para*-isomerides formed in these reactions have also been measured, thus enabling partial rate factors to be calculated. The values obtained are discussed with reference to free valence numbers calculated by the molecular-orbital method.

THE determination of partial rate factors for the homolytic phenylation of nitrobenzene and chlorobenzene was reported in Parts I, II, and III (Hey, Nechvatal, and Robinson, *J.*, 1951, 2982; Augood, Hey, and Williams, *J.*, 1952, 2094; *loc. cit.**), and these and other results were discussed by Hey and Williams (*Discuss. Faraday Soc.*, 1953, **14**, 216). In the present work the survey of homolytic aromatic substitution in the halogenobenzenes is completed by the determination of partial rate factors for the phenylation of fluorobenzene, bromobenzene, and iodobenzene.

* Part III, *J.*, 1953, 44.

The phenylation of bromobenzene by means of the Gomberg reaction, with aryldiazoic acids, was studied in a qualitative manner by Gomberg and Bachmann (*J. Amer. Chem. Soc.*, 1924, **46**, 2339), who isolated 2- and 4-bromodiphenyls from the reaction between bromobenzene and diazotised aniline. The same orientation was observed with $MeO_2C{\cdot}C_6H_4{\cdot}$ radicals derived from methyl *p*-aminobenzoate and from methyl anthranilate by Heilbron, Hey, and Wilkinson (*J.*, 1938, 113), and with *p*-tolyl radicals derived from *p*-toluidine by Gomberg and Pernert (*J. Amer. Chem. Soc.*, 1926, **48**, 1372). Some *meta*-substitution was observed in bromobenzene by France, Heilbron, and Hey (*J.*, 1938, **1364**), who used 4-diphenylyl radicals derived from 4-nitrosoacetamidodiphenyl. The arylation of fluorobenzene and iodobenzene has not been investigated. The proportions of isomerides isolated from these preparative experiments differ widely from those found in the present investigation, in which the mixtures of substituted diphenyls were analysed by infra-red spectroscopy. The reason for these discrepancies is that, as pointed out in Part III (*loc. cit.*), the 4-substituted diphenyls are less soluble and are higher-melting substances than the 2- and the 3-isomerides, and hence, in preparative experiments, are isolated preferentially, and losses of the 2- and 3-isomerides are very substantial. The results of Dannley (personal communication), however, who has measured by ultra-violet spectroscopy the proportion of isomerides obtained in the phenylation of bromobenzene, are in agreement with those reported in the present paper.

Experimental Methods and Results

Direct Determination of ${}^{PhF}_{PhNO_2}K$.—Benzoyl peroxide (6 g.) was allowed to decompose in an equimolar mixture (200 ml.) of nitrobenzene and fluorobenzene in a thermostat at 80° for 72 hr. The mixed product was isolated from the reaction mixture and analysed by estimation of the nitro-compound by titration with titanous chloride. The standard procedure described in Part II (*loc. cit.*) was employed. The results are given in Table 1. Fore-runs, *i.e.*, mixed fractions containing nitrobenzene and fluorodiphenyls, were collected separately from the diaryl fractions, so that the latter should not be contaminated with the last traces of nitrobenzene. The fore-runs were analysed for fluorine, and a correction in terms of fluorodiphenyls

Table 1.*

Expt. No.	Diaryl fraction, g.	Nitro-diphenyl, %	Fore-run, g.	F (%) in fore-run	Correction C_6H_4PhF, mg.	Corr. wt. of diaryl fraction, g.	Nitro-diphenyl, % (corr.)	${}^{PhF}_{PhNO_2}K$	Benzoic, acid, g.	$(Ph{\cdot}CO_2)_2$ accounted for, %
1	2·993	88·84	1·390	3·5	441	3·434	77·43	0·34	2·673	81·1
2	2·951	92·98	2·065	2·9	543	3·494	78·52	0·33	2·594	80·2

Hence, ${}^{PhF}_{PhNO_2}K = 0{\cdot}34$.

* Analyses for fluorine were carried out through the courtesy of Professor M. Stacey, F.R.S., of the University of Birmingham, to whom the authors express their thanks.

applied to the composition of the diaryl fraction. It may safely be assumed that the fore-runs contained no nitrodiphenyls, since these were found not to distil until a temperature 60° above that at which the fore-runs were collected had been reached.

Direct Determination of ${}^{PhBr}_{PhNO_2}K$ *and* ${}^{PhI}_{PhNO_2}K$.—Experiments 3, 4, and 5 were carried out with benzoyl peroxide (6 g.) in an equimolar mixture (200 ml.) of bromobenzene and nitrobenzene, and experiments 6 and 7 with benzoyl peroxide (6 g.) in an equimolar mixture (200 ml.) of iodobenzene and nitrobenzene. The reactions were allowed to proceed in a thermostat at 80° for 72 hr. The isolation and analysis of the mixed products were carried out by the standard procedure described in Part II (*loc. cit.*), except that the fore-runs taken from experiments 6 and 7 were analysed for nitrobenzene by the titanous chloride method, corrections in terms of iododiphenyl being obtained by difference. The results are given in Tables 2 and 3.

Determination of Ratios of Isomerides.—The standard procedure outlined in Part II (*loc. cit.*) was used for the isolation of the diaryl fraction from the products of reactions 8—13. In the pairs of experiments 8 and 9, 10 and 11, 12 and 13, 200 ml. of fluoro-, bromo-, and iodo-benzene respectively were used, together with 6, 8, and 6 g. of benzoyl peroxide. All the reactions were allowed to proceed for 72 hr. in the thermostat at 80°.

For the infra-red spectrographic analysis of the mixtures of the 2-, 3-, and 4-halogenodiphenyls, a Grubb–Parsons instrument was used with an automatic pen recorder. In order to determine for each compound the range in which suitable absorption bands occur and

TABLE 2.

Expt. No.	Diaryl fraction, g.	Nitrodiphenyl, %	Forerun, g.	Br (%) in forerun	Correction C_6H_4PhBr, mg.	Corr. wt. of diaryl fraction, g.	Nitrodiphenyl, % (corr.)	$^{PhBr}_{PhNO_2}K$	Benzoic acid, g.	$(Ph{\cdot}CO_2)_2$ accounted for, %
3	3·915	67·24	0·325	1·96	19	3·934	66·92	0·422	2·73	83·0
4	3·800	69·42	1·738	5·4	274	4·074	64·75	0·465	2·80	85·4
5	3·963	68·18	0·875	3·61	92	4·055	66·63	0·428	—	84·8

Hence $^{PhBr}_{PhNO_2}K = 0{\cdot}44$.

TABLE 3.

Expt. No.	Diaryl fraction, g.	Nitrodiphenyl, %	Forerun, g.	$PhNO_2$ (%) in forerun	Correction C_6H_4PhI, mg.	Corr. wt. of diaryl fraction, g.	Nitrodiphenyl, % (corr.)	$^{PhI}_{PhNO_2}K$	Benzoic acid, g.	$(Ph{\cdot}CO_2)_2$ accounted for, %
6	3·447	62·64	0·698	96·72	23	3·470	62·22	0·432	3·52	89·5
7	3·436	61·08	0·453	91·39	39	3·475	60·39	0·466	3·49	88·8

Hence $^{PhI}_{PhNO_2}K = 0{\cdot}45$.

so to enable a solvent to be chosen, the spectra of the three pure isomerides were measured. 2-, 3-, and 4-Fluorodiphenyl, 4-bromodiphenyl, and 4-iododiphenyl were used as crystalline powders in Nujol mulls, and 2- and 3-bromodiphenyl and 2- and 3-iododiphenyl, which were liquids, were used as capillary films between rock-salt plates. The frequencies of the absorption bands of the nine compounds investigated are given in Table 4.

For all the 2-isomerides, the strong absorption band, which would otherwise be suitable for their estimation, lies very close to a band common to all three isomerides, and hence could not be used. The mixtures were therefore analysed for the 3- and the 4-isomerides only, and the amounts of the 2-isomerides obtained by difference. This procedure had already been adopted for the analysis of mixtures of 2-, 3-, and 4-chlorodiphenyls (Part III, *loc. cit.*). The bands which were used for these estimations were: for 3- and 4-fluorodiphenyl, 876·5 and

TABLE 4.

Diphenyl	Absorption frequency, $cm.^{-1}$	Diphenyl	Absorption frequency, $cm.^{-1}$	Diphenyl	Absorption frequency, $cm.^{-1}$
2-Fluoro-	821·5, 774,* 760·3 *	2-Bromo-	768 *, 759 *	2-Iodo- ...	773,* 754 *
3-Fluoro-	876·5,* 766·3 *	3-Bromo-	884, 793·5,* 776·5,* 759 *	3-Iodo- ...	886·5, 795,* 759 *
4-Fluoro-	843·7,* 760 *	4-Bromo-	834·5,* 764,* 750	4-Iodo- ...	833,* 767,* 748

* Strong absorption.

843·7 $cm.^{-1}$, for 3- and 4-bromodiphenyl 793·5 and 834·5 $cm.^{-1}$, and for 3- and 4-iododiphenyl 795·0 and 833·0 $cm.^{-1}$. Nitromethane was a suitable solvent for all the compounds, having no absorption bands in the region concerned. The determination is most accurate when absorption is between 50% and 65%. The concentrations of the solutions employed (in g./10 ml.), which absorbed radiation to this extent at the wave-lengths concerned, were as follows: 3-Fluorodiphenyl, 0·4012; 4-fluorodiphenyl, 0·3934; 3-bromodiphenyl, 1·4152; 4-bromodiphenyl, 0·6105; 3-iododiphenyl, 1·6023; 4-iododiphenyl, 0·2534. With the iododiphenyls the accuracy of the determination is diminished because of the relative insolubility of the 3- and 4-isomerides, *e.g.*, 0·2534 g. of 4-iododiphenyl in 10 ml. of nitromethane represents an almost saturated solution and it absorbs radiation to the extent of less than 50%. The amount of the 2-isomeride obtained by difference thus shows a cumulative error.

In order to check the accuracy of the determination, the spectra of test solutions containing known amounts of 2-, 3-, and 4-isomerides of the substituted diphenyls were recorded, and their compositions calculated by the method described in Part III (*loc. cit.*). Two such determinations were carried out for each set of isomerides, making six in all. The results were satisfactory in each case; *e.g.*, mixture (*b*) of fluorodiphenyls contained 41% of the 2-, 30% of the 3-, and 29% of the 4-isomeride, while spectrographic analysis gave 41, 31, and 28%, respectively.

The spectra of standard solutions in nitromethane of the diaryl fractions isolated from experiments 8—13 were then recorded, and the compositions of the mixtures calculated. The results are given in Table 5.

TABLE 5. *Analysis of products obtained in phenylation of fluorobenzene, bromobenzene, and iodobenzene.*

Expt. No.	Compound	Composition, % 2-	3-	4-	Expt. No.	Compound	Composition, % 2-	3-	4-	Expt. No.	Compound	Composition, % 2-	3-	4-
8	PhF	53·3	31·5	15·2	10	PhBr	49·7	33·0	17·3	12	PhI	51·5	31·7	16·8
9	,,	54·9	30·0	15·1	11	,,	48·9	33·7	17·4	13	,,	51·9	31·5	16·6
	Mean	54·1	30·7	15·2		Mean	49·3	33·3	17·4		Mean	51·7	31·6	16·7

Reagents.—Nitromethane (Light & Co.) was dried ($CaCl_2$), refluxed in a stream of nitrogen, refluxed over animal charcoal, and twice fractionally distilled through a 4-foot helix-packed column (b. p. 101°/760 mm.). Fluoro-, bromo-, and iodo-benzene (B.D.H.) were washed with concentrated sulphuric acid until the washings were colourless, then with aqueous sodium hydrogen carbonate, and finally with water. After drying ($CaCl_2$), they were twice fractionally distilled as above and had b. p. 85°/760 mm., 156°/760 mm., and 83°/20 mm., respectively. Specimens of 2-, 3-, and 4-fluorodiphenyl, kindly given by Mr. A. C. Littlejohn, to whom the authors express their thanks, were crystallised to constant m. p. from aqueous ethanol; m. p.s were 73·5°, 27°, and 74·5°, respectively.

2-Bromodiphenyl was prepared by a modification of Zaheer and Faseeh's method (*J. Indian Chem. Soc.*, 1944, **21**, 47), which involves diazotisation of 2-aminodiphenyl in hydrochloric acid and decomposition of the diazonium chloride with cuprous bromide. This was found to yield a mixture of 2-chloro- and 2-bromo-diphenyl. The following procedure, however, was satisfactory. A solution of 2-aminodiphenyl (12 g.) in hot constant-boiling hydrogen bromide (21 g., 3 equivs.) was diazotised at 5° with a solution of sodium nitrite (6 g.) in water (10 ml.). Excess of nitrous acid was removed at the end of the reaction by adding urea and stirring the mixture for 20 min. The diazotised solution was added dropwise to a solution of cuprous bromide (from 15 g. of copper sulphate) in constant-boiling hydrogen bromide (20 ml.) with vigorous stirring. The mixture was set aside for 20 min., after which the brown complex was decomposed by warming it on a steam-bath for 2 hr. The dark oil which separated was extracted with ether, and the extract filtered through glass-wool, washed with water, dilute sodium hydroxide, and water again, and dried ($CaCl_2$). Evaporation of the ether, and distillation, gave a pale yellow oil (7 g.), b. p. 146—152°/12 mm. This was dissolved in benzene, passed through alumina, and subsequently eluted with benzene. The solvent was removed and the product distilled under vacuum to give 2-bromodiphenyl as a colourless oil, b. p. 148—150°/10 mm., n_D^{20} 1·6270.

3-Bromodiphenyl was prepared in 13% yield by means of a Gomberg reaction from diazotised *m*-bromoaniline and benzene (Marvel, Ginsberg, and Mueller, *J. Amer. Chem. Soc.*, 1939, **61**, 77). The crude product was redistilled, dissolved in benzene, passed through alumina, and subsequently eluted with benzene. After removal of the solvent the 3-bromodiphenyl was obtained as a colourless oil, b. p. 103°/0·2 mm., n_D^{20} 1·6405.

4-Bromodiphenyl was prepared by Gomberg and Bachmann's method (*Org. Synth.*, **1**, 113) from diazotised *p*-bromoaniline and benzene. It was crystallised to constant m. p. (89·7°) from ethanol.

2-Iododiphenyl was prepared from 2-aminodiphenyl by diazotisation and treatment with potassium iodide (Zaheer and Faseeh, *loc. cit.*). The orange-coloured oil was twice fractionally distilled under vacuum, yielding a pale yellow liquid, b. p. 94—95°/0·07 mm., n_D^{20} 1·6620.

3-Aminodiphenyl (23 g.), dissolved in 5·5N-hydrochloric acid (30 ml.), was diazotised with sodium nitrite (11·5 g.). After 30 min.' stirring to allow the reaction to become complete, a solution of potassium iodide (35 g.) in water (200 ml.) was added dropwise with stirring. Stirring was continued for 1 hr. in the cold and then for 1½ hr. on a steam-bath. The black oil which separated was extracted with ether, and the extract washed with sodium thiosulphate solution, water, sodium hydroxide (three times), and water (twice), and dried ($CaCl_2$). After removal of the ether, 3-iododiphenyl was distilled three times under vacuum and obtained as a colourless oil, b. p. 114·5°/0·3 mm., in 50% yield.

4-Iododiphenyl was prepared in a similar manner from 4-aminodiphenyl (B.D.H.). The crude product, which was obtained as a yellow solid in 70% yield from the distillation, was purified by dissolving it in benzene and shaking the solution with successive portions of concentrated sulphuric acid until the benzene layer was no longer coloured. This was then washed

with aqueous sodium hydrogen carbonate, and with water. After removal of the solvent the product was crystallised to constant m. p. from ethanol, and gave 4-iododiphenyl in white plates, m. p. 113·8°.

Benzoyl peroxide (May & Baker) was purified according to the procedure described in Part II (*loc. cit.*).

Discussion

Partial Rate Factors.—The rates of phenylation of fluorobenzene, bromobenzene, and iodobenzene relative to that of benzene may be computed from the results of the determination of the rates of phenylation relative to that of nitrobenzene (Tables 1, 2, and 3), and the rate of phenylation of nitrobenzene relative to benzene, the determination of which was reported in Part II (*loc. cit.*). The values of ${}^{PhF}_{PhH}K$, ${}^{PhBr}_{PhH}K$, and ${}^{PhI}_{PhH}K$ so obtained, together with the mean values obtained by spectrographic analysis for the ratios of isomerides formed in the phenylation of fluoro-, bromo-, and iodo-benzene (Table 5), enable the calculation to be made of partial rate factors for the phenylation of these compounds. These values, together with the total rates of phenylation relative to benzene, are given in Table 6. The corresponding quantities relating to the phenylation of chlorobenzene, the determination of which was reported in Part III (*loc. cit.*), are included for comparison.

Table 6. *Partial rate factors for the phenylation of the halogenobenzenes.*

Compound PhX	F_o	F_m	F_p	${}^{PhX}_{PhH}K$	Compound PhX	F_o	F_m	F_p	${}^{PhX}_{PhH}K$
Fluorobenzene ...	2·20	1·25	1·20	1·35	Bromobenzene ...	2·59	1·75	1·83	1·75
Chlorobenzene.....	2·7	1·03	1·2	1·44	Iodobenzene	2·79	1·70	1·80	1·80

It may be noted that in all four halogenobenzenes all the positions are activated towards attack by phenyl radicals, and that the activation is greatest in the *o*-position. The *amounts* of the isomerides formed vary in the order $o > m > p$ in all four compounds. In addition, the overall activation of the nucleus towards homolytic attack increases in the order PhF < PhCl < PhBr < PhI. This is in contrast with the results obtained in electrophilic substitution of halogenated aromatic hydrocarbons. It has been found, both for the nitration of the halogenobenzenes (Bird and Ingold, *J.*, 1938, 918) and for the bromination in the 4-position of the 1-halogenonaphthalenes (de la Mare and Robertson, *J.*, 1948, 100), that the chloro- and bromo-compounds react more slowly than either the corresponding fluoro- or iodo-derivatives. Thus, in ascending the series of the halogens, the rates of substitution pass through a minimum, and sequences of the type PhF > PhCl > PhBr < PhI are obtained. This is understandable, because both inductive electron *attraction* and tautomeric electron *repulsion* vary in the order F > Cl > Br > I. The fact that an undisturbed order is obtained for the rates of homolytic substitution in the halogenobenzenes therefore demonstrates that substitution of this type is not susceptible to electrostatic influences on the charge distributions in these molecules. It may also be noted that whereas the *meta*-positions of the halogenobenzenes are completely deactivated towards heterolytic halogenation and nitration, these positions are activated towards homolytic phenylation.

Comparison with Theoretical Predictions.—Atom localisation energies, from which partial rate factors may be calculated directly, have been calculated by Wheland (*J. Amer. Chem. Soc.*, 1942, **64**, 900) for chlorobenzene only. These were discussed in Part III (*loc. cit.*), where the surprisingly good agreement between them and the experimentally-determined partial rate factors was noted. No values of atom localisation energies are available for comparison with the partial rate factors for the other halogenobenzenes.

Free valence numbers, which are related to partial rate factors for homolytic substitution by the relation

$$\log F_r = 2x\beta(f_r - f_b)/2{\cdot}303RT$$

(cf. Brown, *Quart. Reviews*, 1952, **6**, 63), where F_r is the partial rate factor for homolytic substitution at the *r*th position of the molecule, f_r is the free valence at that position, f_b is the free valence at any position in benzene, and $x\beta$ is the change in the resonance integrals β_{rm}, β_{rn}---- brought about by the reagent. Since $x\beta$ is not known, partial rate factors cannot be calculated directly from free valence numbers, though qualitative comparisons can be made, since $\log F_r \propto f_r - f_b$. Sandorfy (*Bull. Soc. chim.*, 1949, **16**, 615) has calculated

free valence numbers in molecules of the type C_6H_5X, using various values for the parameters α_X (the coulomb integral of the atom X), and β_{C-X} (the resonance integral of the C–X bond). The calculations predict the activation of all three positions towards homolytic attack, and show that the *ortho*-position is expected to be the most reactive. The values chosen by Sandorfy for α_X and β_{C-X} for fluorine, chlorine, bromine, and iodine lead to a small increase in the reactivity of the nucleus towards homolytic attack in the order $F < Cl < Br < I$, in agreement with the experimental determinations.

Thanks are accorded to the Department of Scientific and Industrial Research for the awards of Maintenance Grants (to D. R. A. and J. I. G. C.), to the Chemical Society for the award of a Research Grant (to G. H. W.), and to Dr. W. C. Price for providing facilities for the infra-red measurements.

KING'S COLLEGE (UNIVERSITY OF LONDON),
STRAND, LONDON W.C.2.

[*Received, May 28th,* 1953.]

684. *Steric Hindrance in Analytical Chemistry. Part II.* The Interaction of Ferrous Salts with 2-Substituted* 1 : 10-*Phenanthrolines.*

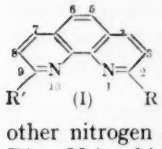
By H. IRVING, M. J. CABELL, and D. H. MELLOR.

Although 2-methyl-1 : 10-phenanthroline ($pK = 5{\cdot}42$) is a stronger base than 1 : 10-phenanthroline ($pK = 4{\cdot}96$) it forms weaker complexes with ferrous ions ($\log K_1 = 4{\cdot}2$, $\log K_2 = 3{\cdot}7$, and $\log K_3 = 2{\cdot}9$). This difference in behaviour is due to steric hindrance to co-ordination which increases with further substitution to such an extent that 2 : 9-dimethyl-1 : 10-phenanthroline will not form complexes with Fe^{II} although it does so with Cu^{I}.

Tris-complexes predominate in the strongly red solutions formed by equivalent amounts of Fe^{++} and 1 : 10-phenanthroline. Corresponding solutions of Fe^{++} and 2-methylphenanthroline are feebly yellow and contain principally the bis-complex. That perchlorate ions precipitate tris-complexes from either solution can be explained quantitatively from considerations of the stability constants of the respective complex ions and the measured solubility products of their perchlorates.

1 : 10-PHENANTHROLINE ("phenan"; I; R = R′ = H) with ferrous salts gives a series of compounds containing the stable red ion $Fe(phenan)_3^{++}$ which is of great analytical importance. The diamagnetism of its salts indicates that the organic components are held by octahedral d^2sp^3 hybrid orbitals. The coplanar resonating system formed by the three aromatic rings of each phenanthroline molecule and the five-membered ring which it forms with the central iron atom is thus repeated in three atomic planes at right angles, and the asymmetry of the resulting structure has recently been confirmed by a successful resolution (Dwyer and Gyarfas, *J. Proc. Roy. Soc. N.S.W.*, 1949, **83**, 263). The considerable optical stability of the enantiomorphous tris-1 : 10-phenanthroline ferrous ions ($t_{\frac{1}{2}} = 121$ min. at 15°; Dwyer, personal communication) is in keeping with the slow rate of exchange with the radio-nuclide ^{59}Fe ($t_{\frac{1}{2}} = 100$ min.; Ruben, Kamen, Allen, and Nahinsky, *J. Amer. Chem. Soc.*, 1942, **64**, 2297) and the high over-all stability constant, since $K_3 = [Fe\ phenan_3^{++}]/[Fe^{++}][phenan]^3 = 2 \times 10^{21}$ (Kolthoff, Lee, and Leussing, *ibid.*, 1948, **70**, 2348).

On the other hand, Pfeiffer and Christeleit (*J. pr. Chem.* 1938, **151**, 127) commented on the fact that 2-methyl-1 : 10-phenanthroline ("mephenan"; I; R = Me, R′ = H) forms sparingly soluble complex salts $[Fe(mephenan)_3](ClO_4)_2$ and $[Fe(mephenan)_3]SO_4,12H_2O$, which are only orange-coloured in contrast to the deep red of the corresponding 1 : 10-phenanthroline complexes, and in agreement with McCurdy and Smith (*Analyst*, 1952, **77**, 846) we have found that the introduction of a second methyl group adjacent to the other nitrogen atom produces a compound, 2 : 9-dimethyl-1 : 10-phenanthroline (I; R = R′ = Me), which shows no tendency to form complexes with ferrous ions (cf. Case, *J. Amer.*



(I)

* Part I, Irving, Ring, and Butler, *J.*, 1949, 1489.

Chem. Soc., 1948, **70**, 3994). Indeed, while as little as 2 p.p.m. of ferrous iron give a strongly red solution with $2{\cdot}5 \times 10^{-4}$M-1 : 10-phenanthroline at pH 3—9 (absorbancy = 0·40 in a 1-cm. cell at $\lambda_{max.}$ 510 mμ; cf. Moss and Mellon, *Ind. Eng. Chem. Anal.*, 1942, **14**, 931), we find that replacement of 1 : 10-phenanthroline by 2-methyl-1 : 10-phenanthroline gave a solution with effectively 100% transmittancy over the range 290—600 mμ when measured against a blank containing no iron, and the ferrous concentration had to be increased twenty-fold before a visible yellow colour was produced. Similar weak yellow colours were observed when 1 : 10-phenanthroline was replaced by an equivalent amount of the 2-chloro-compound (cf. Halcrow and Kermack, *J.*, 1946, 155).

This decrease in absorbancy produced when there are substituents α to the nitrogen atoms of 1 : 10-phenanthroline might be due (i) to lower molecular extinction coefficients of the tris-complexes, (ii) to their presence in lower concentration as a consequence of smaller overall stability, or (iii) to a combination of both factors. We have examined these various possibilities.

The synthesis of 2-methylphenanthroline (I; R = Me, R′ = H) by a Doebner–Miller reaction between 8-aminoquinoline and crotonaldehyde gave poorer yields than a Skraup

FIG. 1. *The absorbancy of mixtures of* $5{\cdot}9 \times 10^{-5}$M-*2-methylphenanthroline in an acetate buffer of* pH 4·7 *containing respectively* 20, 40, 80, *and* 160 *p.p.m. of ferrous iron.*

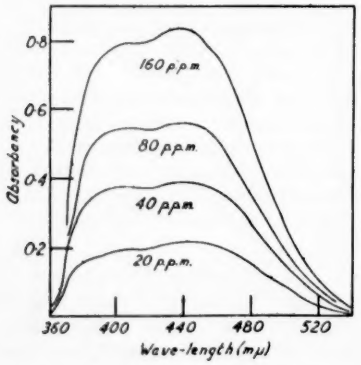
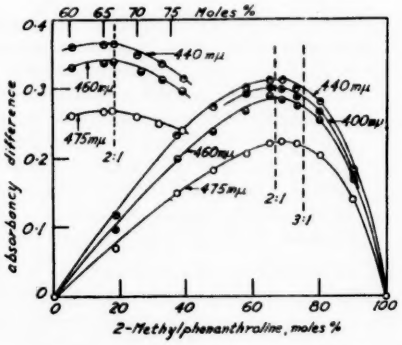


FIG. 2. *The formula of the complex formed by ferrous ions and 2-methyl-1 : 10-phenanthroline—Job's method of continuous variations.*



reaction on 8-aminoquinaldine. The intermediate 8-nitroquinaldine, previously prepared by nitrating quinaldine and separating the 5- and the 8-nitroquinaldine (Gerdeisen, *Ber.*, 1889, **22**, 245), was more conveniently made by condensing *o*-nitroaniline with paraldehyde or, better, crotonaldehyde. 2 : 9-Dimethylphenanthroline was prepared by essentially the method described by Case (*loc. cit.*), and 2-chlorophenanthroline following Halcrow and Kermack (*loc. cit.*).

Fig. 1 shows the absorption spectra of solutions containing varying amounts of ferrous iron and a constant excess of 2-methylphenanthroline in buffers of pH 4·7 containing hydroxylamine; over the spectral range shown the absorbancy of the reagent is negligible. Although the molecular ratio [reagent] : [iron] was varied from 2 : 1 to 16 : 1, the form of the spectra did not change and there was no evidence of the co-existence of more than one absorbing species; for although the broad band in the visible is resolvable into two component bands which almost coalesce, their maxima remain at 400 and 440 mμ respectively, and the relative absorbancies ($\varepsilon_{440}/\varepsilon_{400} = 1{\cdot}05 \pm 0{\cdot}04$) do not vary systematically with composition. The weakness of the complex is shown by the marked deviation from Beer's law.

Since protons compete with ferrous ions for molecules of the basic ligand, complex formation should be favoured by decreasing acidity. Absorbancy data for buffers containing 80 p.p.m. of ferrous iron and a constant 8-fold excess of reagent showed that complex formation was negligible below pH 2·13 and increased linearly with pH over the range 3—4·2.

Solutions of still higher pH could not be studied accurately, for even at pH 4·18 the yellow solution was supersaturated with respect to the very insoluble salt $[Fe(mephenan)_3](ClO_4)_2$ and deposited golden crystals after some hours. At pH 5·14 an immediate yellow turbidity appeared on mixing of the components and, though the solid dissolved readily on warming, crystallization took place during the absorbancy measurements. The composition of the iron complex present in these yellow solutions was next examined spectrophotometrically by the method of continuous variations (Job, *Ann. Chim.*, 1928, **9**, 113; Vosburgh and Cooper, *J. Amer. Chem. Soc.*, 1941, **63**, 437).

Fig. 2 shows how the difference between the measured absorbancy, and that calculated on the assumption that no complex formation has taken place, varies with the mole-fraction of reagent, the sum of the molar concentrations of iron and 2-methylphenanthroline being kept constant throughout at $5·73 \times 10^{-3}$M. The maximum does not occur at 75 mols.% of reagent as expected for a tris-complex, but between 66 and 68 mols.%, suggesting a 2 : 1 complex for which the theoretical value would be 66·67%. In these measurements the buffering proved to have been inadequate, for the pH of various solutions increased over the range 3·7—4·3 with the proportion of base present. Since the extent of complex formation had been shown to increase with pH (see above), this introduced some uncertainty, although the variation of acidity over the crucial composition range 60—80 mols.% was insufficient to account for the observed deviation from the expected maximum at 75 mols.%. A second series of measurements was carried out with slightly less concentrated solutions and at acidities which never fell outside the pH range 4·09—4·11. As shown in Fig. 2 (top left-hand corner), the formation of a bis-complex is confirmed as the predominant species present under the conditions of measurement. The low stability of the complex is the immediate cause of the marked curvature of the Job plots (Fig. 2) which clearly do not lend themselves to the calculation of stability constants, even by the method discussed by Schwarzenbach and Willi (*Helv. Chim. Acta*, 1951, **34**, 528). However, it proved possible to obtain them by the potentiometric titration technique first used by Calvin and Wilson (*J. Amer. Chem. Soc.*, 1945, **67**, 2003) and fully described by Irving and Griffiths (unpublished work).

The absorption spectrum of 2-methylphenanthroline in alkali shows two well-defined bands at $\lambda_{max.}$ 228 and 267 mμ. On acidification they separate slightly and the former suffers a marked decrease in intensity. The absorption of both acid and basic species is negligible in the visible region. The close similarity between the spectrum of 1 : 10-phenanthroline and that of its 2-methyl and 2 : 9-dimethyl derivatives is shown in Table 1. The substances are all monoacid bases and show no tendency to take up a second proton even in strongly acid solutions (cf. Lee, Kolthoff, and Leussing, *loc. cit.*).

TABLE 1. *Absorption spectra of* 1 : 10-*phenanthroline and its methyl derivatives.*

		In acid solution :			In alkaline solution :		
1 : 10-Phenanthroline [a, b]		pH 1·5			pH 10·6		
λ (mμ)	—	221	243	272	229	242	264
10^{-4} ε	—	3·09	0·68	2·99	4·3	0·93	2·94
2-Methylphenanthroline [a]		pH 1·05			pH 10·0		
ε (mμ)	—	221	243	277	228	244	267
10^{-4} ε	—	3·35	0·51	2·85	4·5	1·06	2·95
2 : 9-Dimethylphenanthroline [c]		pH 1·0			pH 5·1		
λ (mμ)	201	222	—	282	224	—	272
10^{-4} ε	4·02	3·84	—	2·99	4·28	—	2·70

[a] Present authors. [b] Compare Kruse and Brandt, *Anal. Chem.*, 1952, **24**, 1307; Fielding and Le Fèvre, *J.*, 1951, 1811, report 10^{-4} ε = 4·07, 0·40, and 2·69 at λ 230, 242, and 264 mμ, respectively, in ethyl alcohol. [c] McCurdy and Smith, *loc. cit.*; solutions in aqueous alcohol.

Despite the relatively small influence of pH upon the absorption spectrum of 2-methylphenanthroline, the value $K_a = [mephenan]\{H^+\}/[mephenanH^+] = 5·3 \pm 0·1$ at 17° was obtained for its acid dissociation constant from measurements of the absorbancy of solutions of constant concentration in a series of buffers (cf. Irving, Ewart, and Wilson, *J.*, 1949, 2672; Phillips and Merritt, *J. Amer. Chem. Soc.*, 1948, **70**, 410). The more accurate value of $pK_a = 5·42$ was obtained from a potentiometric titration of a 0·01M-solution in

0·1M-potassium chloride at 25°. Under the same conditions the dissociation constant of 1 : 10-phenanthroline itself was found to be $1{\cdot}1 \times 10^{-5}$, confirming the values $1{\cdot}2 \times 10^{-5}$ (potentiometric) and $1{\cdot}1 \times 10^{-5}$ (conductimetric) given by Lee, Kolthoff, and Leussing (*loc. cit.*) rather than those of Albert and Goldacre ($5{\cdot}4 \times 10^{-5}$ at 20°; *J.*, 1946, 706; 1948, 2240) or Dwyer and Nyholm ($0{\cdot}63 \times 10^{-5}$; *Proc. Roy. Soc. N.S.W.*, 1946, **60**, 28).

The formation of a tris-complex, ML_3, will proceed through a series of step-reactions

$$Fe^{++} + L \rightleftharpoons FeL^{++}; \quad FeL^{++} + L \rightleftharpoons FeL_2^{++}; \quad FeL_2^{++} + L \rightleftharpoons FeL_3^{++}$$

where L represents a molecule of the uncharged ligand base phenanthroline or methylphenanthroline. The complex equilibria existing in solution can be treated in terms of three formation or stability constants, K_1, K_2, and K_3* defined by $K_n = \{FeL_n\}/\{FeL_{n-1}\}\{L\}$, where $n = 1$, 2, or 3; in practice, classical constants can be used with sufficient accuracy if, as in the present experiments, the ionic strength is not high, and is held reasonably constant. The measurement of formation constants in such systems is often carried out by titrating an acidified solution of metal salt with a concentrated solution of the basic ligand (Irving and Griffiths, *loc. cit.*); but in the present instance, owing to the sparing solubility of the heterocyclic base in water, it was necessary titrate with alkali an acidified mixture of a ferrous salt with an equivalent amount of 2-methylphenanthroline. From measurements of the pH in solutions of which the total concentrations C_M of metal, C_H of acid, and C_L of chelating base are known, it is possible to calculate the degree of formation or ligand number, $\bar{n}$, $= (C_L - [L])/C_M$ at corresponding values of [L], the concentration of "free" ligand, *i.e.*, of heterocyclic base bound neither to protons nor to ferrous ions. From the experimental data a formation curve, *i.e.*, a plot of $\bar{n}$ against pL($= -\log_{10}[L]$), can be drawn. Its course (not reproduced) shows clearly that, in addition to mono- and bis-complexes, the tris-complex must participate in the equilibrium when the ligand concentration is high enough; but the formation curve could not be traced much above $\bar{n} = 2{\cdot}3$ owing to the precipitation of basic material above pH ~5·5. However, the equation to the formation curve is known to be (Bjerrum, "Metal Ammine Formation in Solution," Copenhagen, 1941)

$$n + (n-1)K_1[L] + (n-2)K_1K_2[L]^2 + (n-3)K_1K_2K_3[L]^3 = 0$$

and by successive approximations we arrive at the values $\log K_1 = 4{\cdot}2$, $\log K_2 = 3{\cdot}7$, and $\log K_3 = 2{\cdot}9$, of which the last value is the least reliable. The overall stability constant β_3 for the reaction

$$Fe^{++} + 3(\text{mephenan}) \rightleftharpoons Fe(\text{mephenan})_3^{++}$$

is thus given by $\log \beta_3 = \log K_1K_2K_3 = 10{\cdot}8$, which should be compared with the value $\log \beta_3 = 21{\cdot}3$ for phenanthroline itself (Lee, Kolthoff, and Leussing, *loc. cit.*). The lower value supports the second hypothesis proposed on p. 3418, *viz.*, that 2-methyl substitution reduces the strength of the ferrous complexes. 2-Methylphenanthroline ($pK_a = 4{\cdot}96$) is a stronger base than phenanthroline ($pK_a = 5{\cdot}42$), the strength of the proton-complex having increased as expected from the known effect of the methyl group in similar systems. However, the strength of the corresponding metal complexes follows the reverse order, an effect which has been noted in complexes with *N*-substituted ethylenediamines (Irving and Griffiths, *loc. cit.*), and is apparent in other systems where there is marked steric hindrance to complex formation.

There are, however, still more significant differences between the reactions with ferrous iron of phenanthroline and its 2-methyl derivative. For the parent base, $\log K_1$ is only 5·9 (Kolthoff, Leussing, and Lee, *J. Amer. Chem. Soc.*, 1950, **72**, 2173), so the product $\log K_2K_3 = 15{\cdot}4$. Now, in general, there is a progressive decrease in the ease with which successive ligand molecules are co-ordinated to a central ion, *i.e.*, $K_n > K_{n+1}$. But even if we put $\log K_2 = \log K_3 = 7{\cdot}7$ in this case, the value of K_2 so obtained is still appreciably greater than that of K_1; should $\log K_2$ be greater than $\log K_3$, the anomalous inequality $\log K_1 < \log K_2$ will be still greater. 2-Methylphenanthroline, however, follows the normal pattern in its ferrous complexes, with $K_1 > K_2 > K_3$. Indeed, phenanthroline

* For symbolism see *J.*, 1953, 3192, 3397.

itself behaves normally in its complexes with zinc, for which log $K_1 = 6{\cdot}43$, log $K_2 = 5{\cdot}72$, and log $K_3 = 4{\cdot}89$ (*idem, ibid.*, 1951, **73**, 390). The anomalous behaviour of ferrous ions with those phenanthroline derivatives which are *not* sterically hindered will be discussed in a later paper of this series in relation to the accompanying loss of paramagnetism and change in adsorption spectrum. It is believed to be due to orbital stabilisation (Irving and Williams, *Analyst*, 1952, **77**, 813; *J.*, 1953, 3192).

We have yet to explain why perchlorates of a tris-complex can crystallise out from ferrous solutions containing 1 : 10-phenanthroline or its 2-methyl derivative although the evidence of absorption spectrophotometry (see above) points to a bis-complex as the predominant species in solutions of the latter. The composition of any equilibrium mixture of step-complexes is uniquely determined by the concentration of free ligand and the relevant stability constants (Bjerrum, *op. cit.*). Explicitly

$$[ML_n] = C_M\beta_n[L]^n / \sum_0^n \beta_n[L]^n \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $\beta_n = K_1K_2 \ldots K_n$, and $\beta_0 = 1$. Since the iron–phenanthroline system greatly resembles the system iron–2 : 2′-dipyridyl, for which the values log $K_1 = 4{\cdot}2$,

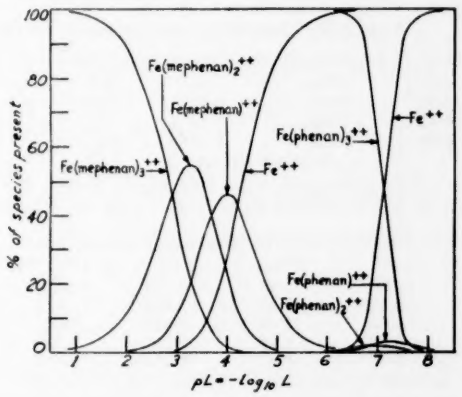


FIG. 3. (L *is* 1 : 10-*phenanthroline or* 2-*methylphenanthroline.*)

log $K_2 < 5$, and log $K_3 > 7{\cdot}3$ have been reported (Baxendale and George, *Trans. Faraday Soc.*, 1950, **46**, 55), we may reasonably assume that the relative values of stability constants in the iron–phenanthroline system follow the same pattern. Taking log $K_1 = 5{\cdot}9$, log $K_2 = 6{\cdot}9$, and log $K_3 = 8{\cdot}5$, we have calculated the relative concentrations of the various species co-existing in solution at various values of pL. It is immediately obvious (Fig. 3) that the complexes Fe(phenan)$^{++}$ and Fe(phenan)$_2^{++}$ have only a very limited range of existence and that they make an almost negligible contribution to the composition of the solution even under optimum conditions. With 2-methylphenanthroline, however, each complex is capable of playing a dominant rôle at an appropriate value of the concentration of free ligand.

Fig. 3 merely shows the *relative proportions* of the various complexes as a function of free ligand concentration. The *absolute* amounts of each in solution will increase with the total concentration of iron, C_{Fe}, and the solution will become saturated and precipitation take place when the solubility of the least soluble salt formed from any of the anions and cations (simple or complex) present in solution is exceeded. In the cases under consideration it is the perchlorates of the tris-complexes which are precipitated in this way; but we emphasise that such behaviour is not a prerogative of the highest complex present, for precipitation of lower complexes, or even of the cation itself, might take place preferentially if, from reasons of lattice energy, their salts with appropriate anions were less soluble than those of higher or lower complexes with the same partner.

The solubility of pure tris-1 : 10-phenanthrolineferrous perchlorate, [Fe(phenan)$_3$](ClO$_4$)$_2$,

in a number of aqueous buffers was readily obtained by withdrawing aliquots of the saturated solution, adding excess of phenanthroline, and making up to a known volume with buffer of pH 4. The absorbancy of the red tris-complex was then measured at 510 mμ, and the iron content calculated from the absorbancy of similar solutions containing the same concentration of reagent and known amounts of ferrous iron. From the experimental value of C_{Fe}, the total concentration of iron in equilibrium with the solid perchlorate, we are able to calculate [L] from the following equations

$$C_L = 3C_{Fe} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$C_L = [FeL^{++}] + 2[FeL_2^{++}] + 3[FeL_3^{++}] + [HL^+] + [L] \quad . \quad . \quad (3)$$

$$C_{Fe} = [Fe^{++}] + [FeL^{++}] + [FeL_2^{++}] + [FeL_3^{++}] \quad . \quad . \quad . \quad . \quad (4)$$

From the known composition of the solid perchlorate taken, we have $[ClO_4^-] = 2C_{Fe}$, so it is possible to evaluate the solubility product defined as $\beta_s = [ML_3^{++}][ClO_4^-]^2$. Results given in Table 2 show that values of β_s obtained from measurements in different buffers are in satisfactory agreement, and that the average value of $p\beta_s = 8{\cdot}56$ for trisphenanthrolineferrous perchlorate is not greatly dependent upon the somewhat arbitrarily chosen values of log K_2 and log K_3.

TABLE 2. *Solubility measurements on the perchlorates of the tris-complexes.*

(*a*) Tris-1 : 10-phenanthrolineferrous perchlorate.

pH	10^1C_{Fe}	pL	$p\beta_s$	pL	$p\beta_s$	pL	$p\beta_s$
3·22	9·35	6·374	8·492	6·994	8·633	6·347	8·490
4·12	8·84	6·149	8·561	6·155	8·530	6·076	8·554
5·02	8·18	5·975	8·665	6·374	8·456	6·854	8·661
	Average values:		8·57 [a]		8·54 [b]		8·57 [c]

[a] By assuming log $K_1 = 5{\cdot}89$, log $K_2 = 6{\cdot}18$, and log $K_3 = 9{\cdot}24$. [b] By assuming log $K_1 = 5{\cdot}87$, log $K_2 = 5{\cdot}00$, and log $K_3 = 10{\cdot}40$. [c] By assuming log $K_1 = 5{\cdot}90$, log $K_2 = 6{\cdot}90$, and log $K_3 = 8{\cdot}50$.

(*b*) Tris-2-methylphenanthrolineferrous perchlorate.

pH	10^3C_{Fe}	pL	10^1Fe^{++}	$p\beta_s$	
4·00	2·23	3·836	4·255	9·786	By assuming log $K_1 = 4{\cdot}2$
4·50	1·59	3·604	1·452	9·840	log $K_2 = 3{\cdot}7$
4·66	1·57	3·511	1·021	9·726	log $K_3 = 2{\cdot}9$
5·32	1·12	3·287	0·285	9·903	Average value: $p\beta_s = 9{\cdot}81$
5·66	0·87	3·276	0·210	9·807	

Saturated solutions of pure ferrous tri-2-methyl-1 : 10-phenanthroline were prepared in a number of buffers and analysed for iron by adding excess of 1 : 10-phenanthroline and making up to a standard volume with a buffer of pH 4 containing hydroxylamine. Under these conditions all the iron is displaced from its weak complexes with 2-methylphenanthroline and transformed into the red tris-1 : 10-phenanthroline complex (ferroin) which was determined absorptiometrically at 510 mμ as before. A direct determination of C_L, and hence an independent check on the validity of equation (2), were also possible in this system, for when aliquots of the saturated perchlorate solutions were diluted 100-fold with 0·1N-hydrochloric acid, the weak complexes were completely resolved into ferrous ions and 2-methylphenanthrolinium ions so that the total amount of base, C_L, could be determined absorptiometrically at wave-lengths where interference from the ferrous ion was negligible.

The remarkably low solubility of trisphenanthrolineferrous perchlorate ($8{\cdot}83 \times 10^{-4}$M; ~0·70 g./l.) has led to its use for the gravimetric determination of perchlorate ions (Brandt and Smith, *Analyt. Chem.*, 1949, **21**, 1313). The solubility of the corresponding tris-2-methylphenanthrolineferrous perchlorate is appreciably lower ($3{\cdot}38 \times 10^{-4}$M; ~0·28 g./l.).

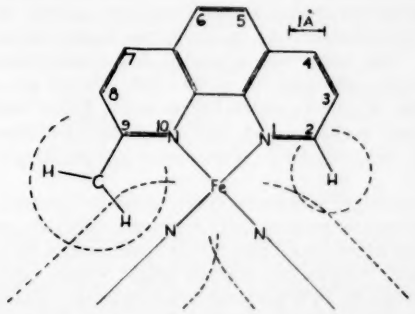
At pH 5·0, the values of pL in saturated solutions of trisphenanthrolineferrous and trismethylphenanthrolineferrous perchlorates are 6·0 and 3·3 respectively. Reference to Fig. 3 and equation (1) shows that in the former case $\bar{n} \sim 3$ and the solution consists essentially of the tris-complex. However, in the case of the methyl derivative, when pL = 3·3 the solution contains at most 22% of the tris-complex with 54% of $Fe(mephenan)_2^{++}$, 21·5% of $Fe(mephenan)^{++}$, and about 2·5% of uncomplexed Fe^{++}. The degree of formation, $\bar{n}$, is only 1·95. In short, owing to a combination of circumstances—the very sparing

solubility of the perchlorate of the tris-complex, the regular progression of the stability constants $K_1 > K_2 > K_3$, and their low absolute value—precipitation takes place when the total concentration of iron in solution is low, and when the principal species is the 1 : 2 complex.

Although $Fe(phenan)_3^{++}$ has the very high molecular extinction coefficient of $\varepsilon = 11,100$ at $\lambda_{max.}$ 510 mμ, the 1 : 1 complex $Fe(phenan)^{++}$ has a broad absorption band with $\varepsilon \sim 330$ at $\lambda_{max.}$ 400—450 (Kolthoff, Leussing, and Lee, *J. Amer. Chem. Soc.*, 1950, **72**, 2173). The absorption band of $Fe(mephenan)_2^{++}$ is also broad (cf. Fig. 1) and an upper limit for its molecular extinction coefficient is found to be $\varepsilon = 900$—1000 at 435 mμ, if contributions from 1 : 1 and 1 : 3 complexes are ignored.

Owing to its sparing solubility in water it was impossible to study the reactions of 2-chlorophenanthroline with ferrous iron under conditions exactly equivalent to those employed with 2-methylphenanthroline. The chloro-compound certainly forms a weak, pale yellow complex with ferrous iron, and the absorption spectrum resembles that of the 2-methyl analogue in having a very broad band with $\lambda_{max.}$ 510. The intensity of absorption is considerably below that given by equivalent amounts of ferrous iron and 2-methylphenanthroline, as would be expected from the similar degree of steric hindrance and the expected lower basicity of the reagent.

FIG. 4.



The effect of steric hindrance in preventing the formation of certain octahedral complexes has already been discussed in connection with the non-formation of the aluminium tris-8-hydroxy-2-methylquinoline complex (Irving, Ring, and Butler, *J.*, 1949, 1489). A similar "packing effect" with 2-substituted 1 : 10-phenanthrolines is readily demonstrated with the aid of models. Fig. 4 represents a section through the plane of one chelate ligand molecule based on conventional van der Waals radii and interatomic distances: the "interference envelope" of the atomic planes formed by the two other ligand molecules at right angles to the first are shown by broken lines. Interference by a single methyl (or halogen) group will clearly lead to distortion of bond lengths and angles with a consequent decrease in stability. With substituents adjacent to only one nitrogen in each ligand, distortion can be minimised if the methyl groups lie in positions as far removed from one another as possible. With substituents adjacent to each nitrogen atom steric hindrance is very greatly increased and complex formation between iron and, *e.g.*, 2 : 9-dimethylphenanthroline appears to be completely inhibited. Annelation in positions 2 : 3 and/or 8 : 9 will, of course, produce the same effect.

Despite their reluctance to co-ordinate to ferrous iron, 2-methyl-, 2-chloro-, and 2 : 9-bis-dimethyl-1 : 10-phenanthroline give strongly coloured complexes with cuprous copper which will be described in a later paper.

EXPERIMENTAL

Preparation of Reagents.—*2-Methyl-1 : 10-phenanthroline* (I; R = Me, R′ = H).—(*a*) Paraldehyde (40 g.) was added during ½ hr. to *o*-nitroaniline (50 g.), concentrated hydrochloric acid (50 g.), and water (15 ml.) with constant stirring. After the reaction had subsided the

mixture was heated for 1 hr. on the water-bath, then cooled, poured into water (2 l.), and made strongly alkaline. After being kept overnight the precipitate was collected and dried. Recrystallization from alcohol (charcoal) gave yellow needles of 8-nitroquinaldine, m. p. 136°. Somewhat better yields were obtained by adding freshly distilled crotonaldehyde (50 g.) to a mechanically stirred mixture of *o*-nitroaniline (190 g.), arsenic pentoxide (82 g.), concentrated sulphuric acid (90 ml.), and water (30 ml.) at such a rate that the initial temperature of 80—90° was maintained without external heating. After a further ½ hour's heating on the water-bath the mixture was rapidly cooled and strongly basified. The tar which was formed was collected and taken up in hot concentrated hydrochloric acid (charcoal), and the filtrate basified. The product after drying was extracted (Soxhlet) with ethyl alcohol, giving 8-nitroquinaldine (34·8 g., 26%), m. p. 136° after recrystallization from aqueous alcohol (Doebner and Miller, *Ber.*, 1884, **17**, 1700, give 137°).

(*b*) 8-Aminoquinaldine (29 g.), obtained in 84% yield by reduction of 8-nitroquinaldine with stannous chloride following Gerdeisen (*Ber.*, 1889, **22**, 245), was mixed with arsenic pentoxide (27·2 g.), water (13·6 ml.), and concentrated sulphuric acid (71 g.) and stirred mechanically under reflux while the temperature was raised to 100° (oil-bath). Anhydrous glycerol (60·5 g.) was added during 15 min., and the temperature raised to 140° and kept there for 2 hr. After being cooled, the mixture was basified at 0° by adding 250 ml. of 40% sodium hydroxide solution. After being kept overnight the viscous brown product which separated was extracted several times with hot benzene, and the combined extracts were dried over pellets of sodium hydroxide. After 12 hr. the dried benzene extracts were decanted, and the solvent removed under reduced pressure. On fractionation *in vacuo* unchanged 8-aminoquinaldine distilled first (b. p. 110°/2 mm.), followed by 2-methylphenanthroline, as a viscous orange liquid, b. p. 180—185°/2 mm., which would not solidify. The latter was taken up in the minimum amount of pure benzene and, after the addition of light petroleum (b. p. 80—100°), moist air was drawn slowly through the solution, whereupon the dihydrate separated as white flocks which, after being collected, washed with light petroleum, and air-dried, had m. p. 53° (Gerdeisen, *loc. cit.*, p. 253, gives 53°) (Found: C, 67·5; H, 6·1; N, 12·1. Calc. for $C_{13}H_{10}N_2,2H_2O$: C, 67·75; H, 6·15; N, 12·2%).

The formation of the sparingly soluble mercuric chloride complex of the base, followed by its decomposition in dilute acid suspension with hydrogen sulphide and isolation of the base as previously described, did not bring about any further purification as judged from the constancy of the absorption spectrum. The *picrate* formed bright yellow crystals, m. p. 216° (Found: N, 16·5. $C_{19}H_{13}O_7N_5$ requires N, 16·6%), from ethyl alcohol. These could only be separated with difficulty from the *picrate* of 8-aminoquinaldine, which formed somewhat deeper orange needles, m. p. 188—189°, from ethyl alcohol (Found: N, 17·9. $C_{16}H_{13}O_7N_5$ requires N, 18·0%). 2-Methylphenanthroline perchlorate formed needles, m. p. 207° (decomp.), on recrystallization from hot dilute perchloric acid (Pfeiffer and Christeleit, *J. pr. Chem.*, 1938, **151**, 127, give m. p. 205—207°).

Formation and Composition of the Yellow Iron–2-Methylphenanthroline Complex.—(a) *Effect of changing the proportions of reagents.* Solutions of pH ~ 4·7 containing respectively 20, 40, 80, and 160 p.p.m. of ferrous iron and with 2-methylphenanthroline : iron concentration ratios of 16 : 1, 8 : 1, 4 : 1, and 2 : 1 were prepared by mixing 5 ml. of 0·36% 2-methylphenanthroline perchlorate, 0·2x ml. of stock ferrous solution (1·7553 g. of "AnalaR" ferrous ammonium sulphate in 250 ml. of metal-free water), and 0·25x ml. of 2·5% hydroxylamine hydrochloride solution (x = 1—4) and making up to 10 ml. with an acetate buffer. Absorption spectra were measured with a Beckman Model DU Spectrophotometer, the smallest slit-widths compatible with reasonable sensitivity being used. The results appear in Fig. 1.

(b) *Effect of changing the acidity.* 3-Ml. portions of a solution containing 0·28 g. of 2-methylphenanthroline perchlorate, 8 ml. of 10% hydroxylamine hydrochloride, and 6·67 ml. of standard iron solution (1000 p.p.m.) in 25 ml. of water were diluted to 10 ml. with a series of buffer solutions. The absorption spectra of these solutions (each containing 80 p.p.m. of ferrous iron, with a concentration ratio of metal : reagent = 1 : 8) were measured against blanks of the same composition save that 6·67 ml. of distilled water had replaced the standard iron solution. Typical values for the absorbancy, A, at λ 430 mμ were:

pH	1·79	2·13	2·54	3·06	3·10	3·64	3·82	4·18	4·43
A (1 cm.)	0·0	0·020	0·058	0·119	0·162	0·385	0·476	0·671	0·672

(c) *Application of the method of continuous variations.* The absorption spectra of mixtures of x ml. of a solution A (0·1227 g. of 2-methylphenanthroline dihydrate in 100 ml. of 0·05M-

potassium hydrogen phthalate buffer of pH 3·97) with $(10 - x)$ ml. of an iron solution B (0·2247 g. of ferrous ammonium sulphate and 1 g. of hydroxylamine hydrochloride in 100 ml. of the same buffer) were measured in 1-cm. Corex cells against a blank containing buffer solution alone. The differences between the experimentally determined absorbancies and those calculated on the basis of simple admixture are given below.

Mol.-fraction of reagent	pH	Absorbancy differences at λ (mμ): 400	425	440	460	475
1·000	4·27	0·048	0·031	0·024	0·017	0·013
0·894	4·15	0·169	0·176	0·183	0·172	0·141
0·796	4·06	0·258	0·266	0·276	0·254	0·204
0·735	4·03	0·286	0·293	0·299	0·274	0·219
0·685	4·00	0·298	0·305	0·312	0·282	0·223
0·651	4·00	0·303	0·304	0·310	0·289	0·219
0·583	3·98	0·291	0·296	0·300	0·265	0·204
0·482	3·86	0·271	0·270	0·272	0·237	0·181
0·376	3·86	0·233	0·233	0·232	0·199	0·151
0·190	3·80	0·116	0·117	0·114	0·096	0·068
0·000	3·72	0·005	0·003	0·002	0·002	0·002

A similar set of measurements with mixtures prepared from solutions A and B after dilution with 3·4 ml. of distilled water and 3·4 ml. of diluted ammonia respectively gave the following results :

Mol.-fraction of reagent	pH	Absorbancy differences at λ (mμ): 400	425	440	460	475
0·000	4·27	0·047	0·031	0·025	0·018	0·017
0·603	4·09	0·352	0·362	0·362	0·329	0·260
0·651	4·09	0·350	0·360	0·365	0·337	0·268
0·664	4·09	0·349	0·357	0·367	0·339	0·269
0·705	4·10	0·333	0·344	0·350	0·325	0·260
0·737	4·10	0·318	0·329	0·337	0·313	0·252
0·767	4·11	0·296	0·396	0·315	0·298	0·240
1·000	4·24	0·016	0·008	0·006	0·004	0·003

Dissociation Constant of the 2-Methylphenanthrolinium Ion.—(a) *Spectrophotometric determination.* 5-Ml. aliquots of a $\sim 2{\cdot}2 \times 10^{-3}$M-solution of the base in water were diluted with an equal volume of sodium acetate–hydrochloric acid or phosphate buffers. The absorbancies measured in a 1-cm. silica cell against the appropriate blanks are given below for four wavelengths :

pH	Absorbancy at λ (mμ): 235	268	275	280	pH	Absorbancy at λ (mμ): 235	268	275	280
1·54	0·265	0·585	0·669	0·629	5·25	0·406	0·600	0·605	0·494
2·40	0·284	0·600	0·687	0·640	5·67	0·420	0·589	0·535	0·430
3·32	0·287	0·570	0·650	0·592	5·94	0·462	0·612	0·533	0·422
4·04	0·290	0·559	0·625	0·561	6·50	0·468	0·612	0·509	0·388
4·48	0·317	0·565	0·619	0·542	7·00	0·491	0·615	0·491	0·372
4·83	0·331	0·573	0·610	0·528	7·20	0·500	0·623	0·495	0·374
5·04	0·359	0·590	0·611	0·514	7·76	0·504	0·634	0·502	0·377

pK_a (calc.) 5·2 5·3 5·4 5·2

Average $pK_a = 5{\cdot}3$ for 17° and an ionic strength of ~0·1M.

(b) *Potentiometric method.* A 0·01M-solution of 2-methylphenanthroline (0·1151 g. of the dihydrate in 50 ml. of 0·1M-potassium chloride containing 0·5 ml. of 0·168N-hydrochloric acid) was titrated potentiometrically in an apparatus (Irving and Griffiths, *loc. cit.*) kept in a thermostat at 25°. After correction for volume changes and buffering by the medium, the value $pK_a = 5{\cdot}42$ at 25·0° ± 0·1° and $\mu = 0{\cdot}1$ was obtained.

Measurement of Stability Constants.—2-Methylphenanthroline dihydrate (0·0691 g.) and ferrous ammonium sulphate (0·0196 g.) were dissolved in 2·44 ml. of 0·164N-hydrochloric acid (which was 0·1M with respect to potassium chloride) and made up to 50 ml. with 0·1M-potassium chloride. All solutions were initially air-free. Exposure to air being avoided, 40 ml. of this solution were transferred to the titration vessel (Irving and Griffiths, *loc. cit.*) and titrated with 0·1016N-hydrochloric acid while being stirred with a stream of nitrogen equilibrated with water vapour by passage through 0·1M-potassium chloride solution at 25°. By using a Cambridge

pH-meter with a saturated calomel–glass-electrode combination previously calibrated with standard buffers, the pH was measured after each addition of base. The solution remained quite colourless up to pH 3, whereat the yellow colour of the complex appeared and deepened with each addition of alkali. Incipient turbidity was noted at pH ~5·6 and precipitation was definite at pH 6·7, at which point small additions of alkali caused large increases in pH. Nevertheless, the solution gave no reaction for ferric iron on the addition of thiocyanate ions. Results of a typical titration are given below together with the corresponding calculated values of the degree of formation, $\bar{n}$, and the free ligand exponent, pL, *i.e.*, the decadic logarithm of the reciprocal of the concentration of 2-methylphenanthroline which is not bound to either proton or ferrous ion.

Vol. of alkali, ml.	pH	pL	$\bar{n}$	Vol. of alkali, ml.	pH	pL	$\bar{n}$	Vol. of alkali, ml.	pH	pL	$\bar{n}$
0·30	2·90	4·747	0·009	1·40	4·04	3·756	1·47	2·10	5·00	3·018	2·33
0·50	3·04	4·633	0·322	1·50	4·18	3·641	1·64	2·30	5·26	2·851	2·36
0·70	3·20	4·481	0·383	1·60	4·32	3·527	1·80	2·40	5·40	2·771	2·30
0·90	3·41	4·294	0·629	1·70	4·46	3·416	1·95	2·50	5·53	2·699	2·23*
1·10	3·64	4·095	0·943	1·80	4·59	3·400	2·14	2·60	5·68	2·628	2·09
1·30	3·91	3·869	1·29	1·90	4·73	3·211	2·20				

* Turbidity apparent.

Under comparable conditions, steady and reproducible potentials were obtained in the titration of ferrous iron in the absence of 2-methylphenanthroline up to pH 4·5. At this point addition of 0·04 ml. of alkali increased the pH abruptly to 6·70, and thereafter the acidity gradually increased and a fine reddish precipitate separated later.

Solubility of Tris-2-methyl-1 : 10-phenanthrolineferrous Perchlorate.—Saturated solutions at acidities between pH 3 and 6 were prepared by warming a suitable sodium acetate–hydrochloric acid buffer mixture to nearly 100° and adding solid complex (prepared according to Pfeiffer and Christeleit, *loc. cit.*, washed with 20% methanol, and dried in a vacuum desiccator to constant weight) until saturated. The solution was then cooled and kept at 25° with occasional shaking for 12 hr. to ensure equilibrium. Samples of the saturated solution were then separated from undissolved solid and analysed for total reagent and total iron as follows: (*a*) Total 2-methylphenanthroline: 0·25 Ml. of the saturated solution was diluted to 25 ml. with 0·1N-hydrochloric acid to decompose the ferrous complex, and the concentration of methylphenanthrolium ion was calculated from the absorbancies at 221, 277, and 310 mμ by comparison with the absorbancy of standard solutions of pure base in 0·1N-hydrochloric acid. It was established that ferrous ions at the concentration present in the analytical samples did not influence the absorbancy due to the 'onium ions. (*b*) Total iron: A measured excess of 1 : 10-phenanthroline was added to a suitable aliquot (0·25 or 0·50 ml.) of saturated solution together with hydroxylamine solution and an acetate buffer of pH 4 to give a total volume of 25 ml. Under these conditions all the iron is converted into the stable trisphenanthroline complex of ferrous iron (ferroin) which was determined absorptiometrically at 510 mμ by reference to absorbancy data obtained similarly from solutions of known iron content.

Solubility of Tris-1 : 10-phenanthrolineferrous Perchlorate.—The preparation of pure perchlorate and of its saturated solutions in aqueous buffers was carried out as above. Since this stable ferrous complex cannot be completely decomposed in 0·1N-acid a direct determination of the concentration of total phenanthroline was not feasible and it was assumed that this was exactly three times that of the ferrous ion. The latter was accurately determined by adding excess of 1 : 10-phenanthroline to 1 ml. of saturated solution and making up to 25 ml. with buffer of pH 4. The measured absorbancy at 510 mμ was then compared with that of solutions of known iron content prepared similarly.

Grateful acknowledgment is made to British Celanese Ltd. for the award of a Senior Studentship to one of us (D. H. M), and to Imperial Chemical Industries Limited for the loan of a Beckman Spectrophotometer.

INORGANIC CHEMISTRY LABORATORY, OXFORD. [*Received, April 22nd*, 1953.]

685. *The Rearrangement of Some Dibromopropyl Esters.*

By W. G. H. Edwards and R. Hodges.

A new rearrangement of dibromopropyl esters is described, in which a simultaneous migration of a bromine atom and an acyloxy-group takes place. The direction and rate of the migration appear to depend on the nature of the acyl group.

The preparation of 1 : 3-dibromo-2-propyl benzoate (I; R = Ph) by the reaction of 1 : 3-dibromopropan-2-ol (II) with benzoyl chloride has been reported by Hurd and Pilgrim (*J. Amer. Chem. Soc.*, 1933, **55**, 1195), but later workers (Andreva and Chernov, *Chem. Abs.*, 1940, 7572) have claimed that it could not be prepared in this way. During other work it became necessary to obtain samples of the benzoates of both of the dibromopropanols (II and III) for infra-red spectral studies. Benzoylation of both dibromopropanols, however, produced the same dibromopropyl benzoate, the products having identical infra-red spectra with their chief maxima at 7·05, 8·5, 9·5, 9·75, and 11·9 μ. In order to decide which of the two possible esters this product represented, it was dehalogenated by catalytic hydrogenation in presence of palladised strontium carbonate, and the infra-red spectrum of the product was compared with the spectra of the two isomeric propyl benzoates (Table 1, *a* and *b*). The debrominated ester was identified as *n*-propyl benzoate, from which it was concluded that the original ester was 2 : 3-dibromopropyl benzoate. It is evident, therefore, that during benzoylation of 1 : 3-dibromopropan-2-ol with benzoyl chloride, a rearrangement to the isomeric dibromopropyl benzoate (IV; R = Ph) takes place.

$CH_2Br{\cdot}CH(O{\cdot}COR){\cdot}CH_2Br$ (I) $\qquad$ $CH_2Br{\cdot}CH(OH){\cdot}CH_2Br$ (II)

$CH_2Br{\cdot}CHBr{\cdot}CH_2{\cdot}OH$ (III) $\qquad$ $CH_2Br{\cdot}CHBr{\cdot}CH_2(O{\cdot}COR)$ (IV)

When acetyl or butyryl chloride was heated with each of the isomeric dibromopropanols, distinct dibromopropyl esters were obtained in each case. The products obtained after catalytic debromination were shown by their infra-red absorption spectra to be the acetates and butyrates of the isomeric propyl alcohols (Table 1; *c*, *d*, *e*, and *f*).

Table 1. *Characteristic infra-red absorption bands of propyl and dibromopropyl esters.*

Ester	$\lambda_{max.}$ for characteristic bands (μ)
a, *iso*Propyl benzoate	8·7, 10·8, 11·75, 12·1
b, *n*-Propyl benzoate	8·6, 10·3, 10·7, 10·95, 11·8
c, *iso*Propyl butyrate	9·55, 12·15
d, *n*-Propyl butyrate	10·0, 10·9, 11·9
e, *iso*Propyl acetate	8·45, 8·7, 9, 10·45
f, *n*-Propyl acetate	8·55, 9·5, 10·25, 13·2
g, 2 : 3-Dibromopropyl benzoate	7·05, 8·5, 9·5, 9·75, 11·9

Table 2. *Variation in characteristic absorption bands of dibromopropyl acetates due to interconversion at* 100°.

Reaction	Absorption (%) of esters 10·25 μ	10·8 μ	11·2 μ	12·2 μ
2 : 3-Dibromopropanol + AcCl; 3 hr.	60	nil	53	nil
2 : 3-Dibromopropanol + AcCl; 36 hr.	52	40	40	28
2 : 3-Dibromopropyl acetate + HCl gas; 84 hr.	50	50	40	30
1 : 3-Dibromopropan-2-ol + AcCl; 3 hr.	48	50	30	34

In all of the acylations described, the reaction time was 1—3 hr., and it seemed possible that the apparent absence of rearrangement during acetylation and butyrylation was due to the rearrangement in these cases being slow. When the time of reaction was prolonged, definite infra-red spectral evidence of the formation of some 1 : 3-dibromo-2-propyl acetate from 2 : 3-dibromopropan-1-ol and acetyl chloride was found (Table 2). When a sample of pure 2 : 3-dibromopropyl acetate was saturated with hydrogen chloride at 20° and heated in a sealed tube at 100° for 36 hr., the product was shown by comparison of

infra-red spectra to be almost wholly the 1 : 3-dibromo-2-propyl ester (Table 2). In the case of the acetates, therefore, the rearrangement takes place in the opposite direction to that of the benzoates, but much more slowly, and it is likely that it is acid-catalysed.

It was at first thought that epibromohydrin might be an intermediate in the rearrangement, according to some such scheme as :

$$CH_2Br{\cdot}CH(O{\cdot}COR){\cdot}CH_2Br \overset{H_2O}{\rightleftharpoons} CH_2Br{\cdot}CH(OH){\cdot}CH_2Br + R{\cdot}CO_2H$$

$$CH_2Br{\cdot}CH(OH){\cdot}CH_2Br \rightleftharpoons HBr + CH_2Br{\cdot}\underset{\diagdown O \diagup}{CH{-}CH_2} \rightleftharpoons CH_2Br{\cdot}CHBr{\cdot}CH_2{\cdot}OH$$

$$\underset{\diagdown O \diagup}{CH_2Br{\cdot}CH{\cdot}CH_2} + R{\cdot}CO^+ + Br^- \longrightarrow CH_2Br{\cdot}CHBr{\cdot}CH_2O{\cdot}COR \text{ [or } CH_2Br{\cdot}CH(O{\cdot}COR){\cdot}CH_2Br\text{]}$$

However, any such mechanism includes the reaction of a carbonium ion or an oxide with a bromine anion, and in the presence of the high concentration of chloride ion present in the reaction mixture, chlorobromopropyl esters should be found in the products. No trace of chlorine could be detected in any of the esters produced, and this mechanism cannot therefore obtain.

When benzoyl chloride was caused to react with an excess of 1 : 3-dibromopropan-2-ol, the products were 2 : 3-dibromopropyl benzoate and unchanged 1 : 3-dibromopropanol. This excludes the possibility that the alcohol rearranges before benzoylation, and it seems that formation of the 2 : 3-dibromopropyl ester takes place by an exceedingly rapid rearrangement of either the 1 : 3-dibromo-2-propyl benzoate or an intermediate complex.

The following mechanism for the rearrangement is proposed :

$$CH_2Br{\cdot}CH(O{\cdot}COPh){\cdot}CH_2Br + H^+ \longrightarrow CH_2Br{\cdot}\underset{\displaystyle HO^+ \diagdown \quad \diagup COPh}{CH}{\cdot}CH_2Br$$

$$CH_2Br{\cdot}\underset{\displaystyle HO^+ \diagdown \quad \diagup O \\ \diagdown \quad \diagup CPh}{\overset{\displaystyle Br \diagdown}{CH}{-}CH_2} \longrightarrow CH_2Br{\cdot}\underset{\displaystyle HO \diagdown \quad \diagup O \\ \diagdown \quad \diagup {}^+CPh}{\overset{\displaystyle Br \diagdown}{CH}{\cdot}CH_2} \longrightarrow H^+ + CH_2Br{\cdot}CHBr{\cdot}CH_2{\cdot}O{\cdot}COPh$$

When Me replaces Ph, the rearrangement takes place in the opposite direction and much more slowly.

Experimental

Preparation of Reference Materials.—1 : 3-Dibromopropan-2-ol was prepared by Fuson and Babcock's method (*Org. Synth.*, **14**, 42).

2 : 3-*Dibromopropanol.* Allyl alcohol (1 mol.) in dry carbon tetrachloride (10 vols.) was treated slowly with bromine (2 mols.) in twice its volume of dry carbon tetrachloride at $<25°$ (ice-cooling). The resulting solution was washed with 2N-sodium carbonate and dried (Na_2SO_4), and the solvent removed by distillation. Fractional distillation of the residue under reduced pressure gave 2 : 3-dibromopropanol, b. p. 116°/15 mm.

n-*Propyl acetate and benzoate, and* iso*propyl acetate and benzoate.* Commercial esters (B.D.H.) were redistilled, fractions used having b. p. 101°, 230°, 81°, and 218°, respectively.

n-*Propyl butyrate and* iso*propyl butyrate.* These esters were prepared by the sulphuric acid-catalysed esterification of the appropriate propanols with butyric acid. *n*-Propyl butyrate had b. p. 142·5°, and *iso*propyl butyrate, b. p. 128°.

Preparation of Dibromopropyl Esters.—The appropriate dibromopropanol (1 mol.) and the acid halide (1·1 mols.) were heated together at 100° for 3 hr. The resulting mixture was diluted with ether, and washed with sodium hydrogen carbonate solution until free from acid, and then with water. After being dried (Na_2SO_4), the ether was evaporated off and the residue distilled under reduced pressure. The product was redistilled under reduced pressure for the preparation of a sample for determination of infra-red spectrum. B. p.s of 1 : 3- and 2 : 3-dibromopropyl esters were identical, *viz.* : acetates, 68°/3 mm.; butyrates, 118°/6·5 mm.; 2 : 3-dibromopropyl benzoate, 165°/3 mm. The isomers were readily distinguishable by their infra-red spectra and those of the propyl esters produced on catalytic dehalogenation.

Catalytic Dehalogenation of Dibromopropyl Esters.—The ester (1 g.) and 2% palladised strontium carbonate catalyst (0·5 g.) in methanol (50 c.c.) were shaken for 24 hr. in hydrogen; absorption was then complete. After filtration and evaporation, distillation gave the propyl ester, which was redistilled for determination of infra-red spectrum. Yields were approx. 80%.

Infra-red spectra were determined on the liquid esters, with a Perkin–Elmer 12.B recording spectrograph.

The authors acknowledge with thanks the interest and advice of Professor F. G. Soper and Professor C. K. Ingold, F.R.S., and the assistance of the Mellor Fund in the provision of apparatus.

CHEMISTRY DEPARTMENT, OTAGO UNIVERSITY,
DUNEDIN, NEW ZEALAND. [*Received, May 29th,* 1953.]

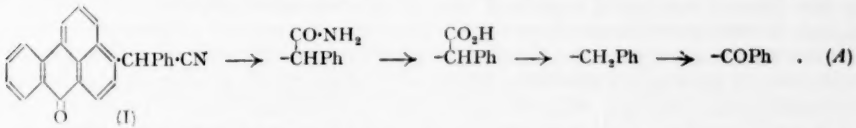
---

686. *The Oxidative Hydrolysis of* 4-α-*Cyanobenzyl*mesobenzanthrone.

By NEIL CAMPBELL and ANTHONY A. WOODHAM.

4-α-Cyanobenzyl*meso*benzanthrone in methanolic potassium hydroxide is converted by oxygen at room temperature into 4-benzoyl*meso*benzanthrone. An intermediate in the reaction is probably 4-benzyl*meso*benzanthrone which under these conditions is very rapidly oxidised to give the benzoyl compound in excellent yield. The mechanism of the reaction is discussed.

4-α-CYANOBENZYL*meso*BENZANTHRONE (I) in methanolic potassium hydroxide is converted by a stream of air into pure 4-benzoyl*meso*benzanthrone (G.P. 568,783; Rule, Campbell, McGregor, and Woodham, *J.*, 1950, 1816). We have now studied the reaction in greater detail with a view to ascertaining its mechanism. A possible course of the reaction is represented by the series (*A*), in which 4-benzyl*meso*benzanthrone, formed from the cyano-compound (I) by successive hydrolysis and decarboxylation, is oxidised to 4-benzoyl*meso*benzanthrone. There is nothing inherently improbable in the first three reactions, especially since we have shown that the amide on hydrolysis with ethanolic potassium hydroxide does in fact give 4-benzyl*meso*benzanthrone. Quite unexpected is



(I) (*A*)

the ready oxidation of the benzyl to the benzoyl compound. It is, of course, well known that methylene groups situated between two aromatic rings can be oxidised to the carbonyl group, but strong oxidising reagents are generally required. Kacer (G.P. 557,249), for example, effected the oxidation in question by hot selenious acid under pressure, and Rule *et al.* (*loc. cit.*) used sodium dichromate and boiling acetic acid. Aerial oxidations of hydrocarbons are also known, but except under forcing conditions they do not occur rapidly and the yields are not high. We have found, however, that 3 min. suffice for the practically quantitative oxidation of 4-benzyl- to 4-benzoyl-*meso*benzanthrone by air in the presence of methanolic potassium hydroxide. A similar result was obtained with 4-*p*-methylbenzyl*meso*benzanthrone. A comparable oxidation to which Professor R. D. Haworth, F.R.S., kindly drew our attention is that of certain 1-benzyl-3 : 4-dihydro*iso*quinolines which are oxidised to benzoyl compounds merely by exposure of their solutions to air (Buck, Haworth, and Perkin, *J.*, 1924, **125**, 2176; see also Lindemann, *Helv. Chim. Acta*, 1949, **32**, 69, Buck, *J. Amer. Chem. Soc.*, 1930, **52**, 3610, and Noller and Wunderlich, *ibid.*, 1952, **74**, 3836). It is doubtful however if these oxidations are effected by air (see, *e.g.*, Tsatsas, *Bull. Soc. chim.*, 1949, 884).

A referee has kindly suggested to us an attractive alternative to the series of reactions (*A*), namely, that the cyano-compound under the influence of alkali is oxidised

to the cyanohydrin and then loses a molecule of hydrogen cyanide to give the benzoyl*meso*-benzanthrone (*B*). We attempted to decide between the schemes *A* and *B* by following

$$\text{R·CHPh·CN} \xrightarrow[O_2]{OH^-} \text{R·C(OH)Ph·CN} \longrightarrow \text{R·COPh} + \text{HCN} \quad . \quad . \quad . \quad . \quad (B)$$

(R = *meso*Benzanthrone radical.)

the fate of the cyano-nitrogen. So far, however, we have not been able to detect more than traces of ammonia (as required by scheme *A*) or hydrogen cyanide (scheme *B*), but we hope soon to examine the reaction more thoroughly.

The aeration of comparable benzyl derivatives in methanolic potassium hydroxide for 10 hr. was studied, but diphenylmethane, fluorene, and dibenzyl gave negative results. We were particularly interested in bis-(*p*-dimethylaminophenyl)methane and 2-benzylpyridine, since the former gives the corresponding benzophenone on mild oxidation with chloranil and 2-benzylpyridine is oxidised merely by exposure to air in ultra-violet light (Muller and Dorfmann, *J. Amer. Chem. Soc.*, 1934, **56**, 2787), but neither compound was oxidised by our method.

Further investigation showed that both aeration and the presence of a base such as potassium hydroxide are essential for the oxidation of the benzyl*meso*benzanthrone, whilst water has an inhibiting effect. These results and the unusual rate of the reaction can be plausibly explained by the formation of a hydroperoxide followed by its base-catalysed decomposition. The formation of a hydroperoxide by the interaction of a reactive methylene group and oxygen in the presence of a base is not surprising, for such reactions are analogous to the well-known carbonyl–methylene condensations (Hock and Lang, *Ber.*, 1944, **77**, 257). Examples of base-catalysed decomposition of peroxides are also known (Kornblum and de la Mare, *J. Amer. Chem. Soc.*, 1951, **73**, 880) and the formation of 4-benzoyl*meso*benzanthrone may well follow a similar course, *viz.* :

$$\text{R·C(H)Ph} \xrightarrow[-BH^+]{B} \text{R·C(:)Ph}^- \xrightarrow{O_2} \text{R·C(O$_2$H)Ph}^- \longrightarrow \text{R·C(=O)Ph} + OH^-$$

(R = *meso*Benzanthrone radical; B = base.)

Efforts to isolate the hydroperoxide, however, met only with slight success. It was noted that the benzoyl compound separated from a solution which was strongly fluorescent although 4-benzoyl*meso*benzanthrone itself does not fluoresce in methanolic potassium hydroxide and this suggests the presence of another product, possibly a hydroperoxide. Acidification of the solution afforded a yellow solid, which gave a positive test for peroxides with starch iodide, but not with chromic acid. Control experiments, however, showed that the starch–iodide test is more sensitive than the perchromic acid test. Hence it was concluded that the solid isolated was not itself a peroxide but contained a peroxide. By measuring the quantity of oxygen absorbed during the oxidation of 4-α-cyanobenzyl- and 4-benzyl-*meso*benzanthrone it was found that 2 atoms of oxygen per molecule were consumed. Unsuccessful efforts were made to oxidise 4-α-cyanobenzyl*meso*benzanthrone by aeration in benzene in the presence of cobalt naphthenate, a catalyst known to promote hydroperoxide formation and decomposition.

4-Benzoyl*meso*benzanthrone when heated with hydroxylamine in pyridine for 8 hr. gives an oxime (II) in which the 7-carbonyl group remains intact. This structure is in harmony with the facts that under the same conditions *meso*benzanthrone forms no oxime; that the red colour of the oxime with sulphuric acid is similar to that given by *meso*benzanthrone, but different from the yellow colour given by *meso*benzanthrone oxime (Campbell and Woodham, *J.*, 1952, 843); and finally that the oxime undergoes the Beckmann transformation to give the anilide of *meso*-benzanthrone-4-carboxylic acid, identical with the anilide obtained by the action of hydrazoic acid on 4-benzoyl*meso*benzanthrone (see below). The last reaction establishes the configuration of the oxime.

R·C(=N·OH)·Ph (II) (R = *meso*Benzanthrone radical.)

We have found that the carbonyl group of *meso*benzanthrone is inert towards hydrazoic

acid (Campbell and Woodham, *loc. cit.*), but 4-benzoyl*meso*benzanthrone gives mainly the anilide of *meso*benzanthrone-4-carboxylic acid (96% yield), whose structure follows from its hydrolysis to *meso*benzanthrone-4-carboxylic acid and aniline. The side-product is *N*-benzoyl-4-*meso*benzanthronylamine.

These results afford another example of an unsymmetrical ketone yielding the same main products by the Beckmann and the Schmidt reaction. It is also noteworthy that the oxime, and presumably the intermediate in the Schmidt reaction (Smith *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 320; 1950, **72**, 2503, 3718; Newman and Gilderhorn, *ibid.*, 1948, **70**, 317), possess the *cis*-configuration, *i.e.*, the hydroxyl and the bulky *meso*benzanthrone group are *cis* to one another.

Experimental

4-α-*Carbamylbenzyl*meso*benzanthrone.*—4-α-Cyanobenzyl*meso*benzanthrone was obtained by the method given in G.P. 501,082 (for details see Woodham, Thesis, Edinburgh, 1951, p. 20). The method is highly capricious. Of twenty-one condensations, seven were reasonably successful, giving yields ranging from 25 to 40%; five yielded traces of the cyanobenzyl-product; two gave a red product; and eight were entirely unsuccessful and afforded only unchanged *meso*benzanthrone. In spite of many experiments we have not succeeded in finding the factor required to give reproducible results, but the temperature seems to be critical, for all the successful condensations were effected at 20° whereas below 18° no condensation occurred.

4-α-Cyanobenzyl*meso*benzanthrone (0·5 g.), in concentrated sulphuric acid (10 ml.) was kept at room temperature for 4 days and then poured into water. The yellow amide was washed free from acid, and crystallised from glacial acetic acid in pale yellow elongated prisms, m. p. 277—280°, which were shown by analysis to be not quite pure (Found: C, 81·5; H, 4·7; N, 4·5. Calc. for $C_{25}H_{17}O_2N$: C, 82·6; H, 4·7; N, 3·9%). The presence of the amido-group was shown by the liberation of ammonia by warm alkali.

The amide (0·1 g.) in 10% ethanolic potassium hydroxide (10 ml.) was boiled until the initial deep green fluorescence disappeared and the evolution of ammonia had practically ceased. The mixture was poured into water (50 ml.) and extracted with ether. Evaporation of the ether gave 4-benzyl*meso*benzanthrone, m. p. and mixed m. p. 177—178°. The same product was obtained by hydrolysis with ethanolic hydrogen chloride.

Attempts to convert the carbamyl group into the carboxyl group by heating the substance with ethanol, sodium nitrite, and concentrated hydrochloric acid gave only 4-benzyl*meso*benzanthrone and some unchanged amide.

Oxidative Hydrolysis Experiments.—4-Benzyl*meso*benzanthrone (0·025 g.) was boiled for 3 min. with methanolic 2N-potassium hydroxide (10·0 ml.) in a current of air. 4-Benzoyl*meso*benzanthrone (yield >90%) separated and, crystallised from benzene, had m. p. and mixed m. p. 175—176°. Similar experiments without alkali gave only unchanged benzyl*meso*benzanthrone.

To a solution of 4-benzyl*meso*benzanthrone (0·02 g.) in methanol (10 ml.) and methanolic 2N-potassium hydroxide (5 ml.) water (3 ml.) was added. A slight separation of the benzyl compound resulted. The solution was boiled and aerated for 35 min. and gave a product which was chiefly unchanged material with a small quantity of 4-benzoyl*meso*benzanthrone.

4-Benzyl*meso*benzanthrone (0·03 g.) was boiled and aerated in methanol (10 ml.) and piperidine (4 ml.) for 10 hr. A pronounced green fluorescence occurred after 30 min. The product was a mixture of unchanged material and 4-benzoyl*meso*benzanthrone.

To measure the quantity of oxygen consumed, experiments were carried out in a 50-ml. gas burette (for details see Woodham, Thesis, Edinburgh, 1951) containing methanolic 2N-potassium hydroxide previously saturated with oxygen. Control experiments showed that 9·9 and 18·6 ml. of oxygen were absorbed after 1 and 2 weeks respectively. Since the burette was sealed at both ends by methanolic potassium hydroxide traps this result must be due to loss of oxygen at the outer surface of the methanol followed by absorption of oxygen at the surface in the reaction bulb. After the necessary corrections had been made the following results were obtained: 4-α-cyanobenzyl*meso*benzanthrone (0·345 g., 1/1000 mol.) after 1 week absorbed 25 ml. of oxygen at N.T.P., and 4-benzyl*meso*benzanthrone (0·320 g., 1/1000 mol.) after 2 weeks absorbed 22 ml. of oxygen. In both cases therefore the benzanthrone compound absorbs approximately 1 mol. of oxygen.

*Oximation of 4-Benzoyl*meso*benzanthrone.*—4-Benzoyl*meso*benzanthrone (1 g.), hydroxylamine hydrochloride (5 g.), and pyridine (50 c.c.) were heated for 8 hr., and the pyridine then

removed by vacuum-distillation. The residue was poured into water and extracted with ether, evaporation of which gave the oxime which, crystallised from ethanol, had m. p. 234—235° (yield 0·83 g.). The oxime was dissolved in benzene and passed down a column of alumina (B.D.H. chromatographic). Development with benzene gave two zones, the lower of which on extraction with ethanol gave the *oxime*, m. p. 245—246° (from ether) (Found: N, 4·0. $C_{24}H_{15}O_2N$ requires N, 4·0%). The above experiment was repeated, but with the heating continued for 50 hr. The crude product on trituration with ether yielded the *dioxime*, yellow crystals, m. p. 246—247° (decomp.) (Found: C, 78·5; H, 4·2; N, 7·8. $C_{24}H_{16}O_2N_2$ requires C, 79·1; H, 4·4; N, 7·7%).

Beckmann Rearrangement of 4-*Benzoyl*meso*benzanthrone Oxime*.—The oxime (0·1 g.) in dry ether (10 ml.) was boiled with phosphorus pentachloride (0·15 g.) for 10 min. Removal of the ether left a brown oil which was triturated with water. Unchanged oxime was removed from the resulting orange solid, and the insoluble portion was extracted with benzene which on evaporation yielded *meso*benzanthrone-4-carboxyanilide, m. p. 268°, undepressed when mixed with a sample prepared as below.

Schmidt Reaction of 4-*Benzoyl*meso*benzanthrone*.—Sodium azide (0·5 g.) was added to 4-benzoyl*meso*benzanthrone (0·5 g.) dissolved in concentrated sulphuric acid (10 ml.). After 3 hr. the solution was poured into water (80 ml.). *meso*Benzanthrone-4-carboxyanilide separated and after being well washed with water to remove sulphate was dried in the oven (yield 0·43 g., 85%; m. p. 265—270°). The *anilide* separated from glacial acetic acid in yellow prisms, m. p. 268—270°, not depressed when mixed with the product of the Beckmann transformation (see above) (Found: C, 81·5; H, 4·6; N, 4·7. $C_{24}H_{15}O_2N$ requires C, 82·5; H, 4·3; N, 4·0%). The anilide (0·3 g.) was boiled for 50 hr. with 60 ml. of a mixture containing equal weights of glacial acetic acid, concentrated sulphuric acid, and water and was then poured into water (450 ml.). The precipitate was extracted with aqueous sodium carbonate in which it was completely soluble and on acidification gave *meso*benzanthrone-4-carboxylic acid (96·5%), m. p. 310—315°, not depressed when admixed with an authentic sample.

The original aqueous acidic liquors were made alkaline with sodium hydroxide and thoroughly shaken with ether. The dried extract on evaporation gave red prisms of 4-amino-*meso*benzanthrone (1%), m. p. 220—222° (lit., 223—224°).

Thanks are expressed to the Anglo-Iranian Oil Company Limited for a grant.

UNIVERSITY OF EDINBURGH. [*Received, April 25th*, 1953.]

---

687. *A Comparison of the Apparent Dipole Moments of the Brominated Methanes dissolved in Benzene with the True Values determined as Gases.*

By A. D. BUCKINGHAM and R. J. W. LE FÈVRE.

New measurements provide the following values for CH_3Br, CH_2Br_2, and $CHBr_3$, respectively: μ_{gas} = 1·82, 1·42, 0·99, and $\mu_{C_6H_6}$ = 1·61, 1·41, 1·02 D. The $\mu_{C_6H_6}/\mu_{gas}$ ratios drawn from these figures fit the equations listed previously by Buckingham and Le Fèvre (*J.*, 1952, 1932) as Nos. 2, 3, and 4 better than they do No. 1.

THIS paper records measurements parallel to those on the chlorinated methanes (Barclay and Le Fèvre, *J.*, 1950, 556) with a view to supplement information concerning small solute molecules (Buckingham and Le Fèvre, *J.*, 1952, 1932; Harris, Le Fèvre, and Sullivan, *J.*, 1953, 1622; Buckingham, Harris, and Le Fèvre, *J.*, 1953, 1626). The results now obtained are summarised in Table 1 under the headings, and with the symbols, used before (see above references).

TABLE 1. *Polarisations at 25°, and dipole moments.*

	CH_3Br	CH_2Br_2	$CHBr_3$		CH_3Br	CH_2Br_2	$CHBr_3$
${}_TP_{gas}$ (c.c.)	82·5	64·3	49·8	$({}_TP_\infty)_{C_6H_6}$	67·7	63·4	50·9
${}_DP$ (c.c.)	14·7	22·9	29·6	${}_DP$ (c.c.)	14·7	22·9	29·6
${}_OP_{gas}$ (c.c.)	67·8	41·4	20·2	$({}_OP_\infty)_{C_6H_6}$	53·0	40·5	21·3
μ_{gas} (D)	1·82	1·42	0·99	$\mu_{C_6H_6}$ (D)	1·61	1·41	1·02

Experimental

Materials.—A B.P.C. sample of methyl bromide was dried by passage through phosphoric oxide, condensed, and redistilled before use, the middle fraction only being taken. Methylene dibromide (*ex* B.D.H.), after being dried ($CaCl_2$), had b. p. 97·2°/755·6 mm. The bromoform, initially a B.P.C. specimen, was dried ($CaCl_2$) and fractionated; b. p. 144·7—145·0°/760 mm. The solvent was prepared by partially freezing "AnalaR" benzene and storing the remelted solid over clean sodium wire.

Measurements on Gases.—The circuit shown as Fig. 3 of the paper by Le Fèvre, Ross, and Smythe (*J.*, 1950, **276**) and the cell assembly illustrated by Le Fèvre, Mulley, and Smythe (*J.*, 1950, 290) were employed with methyl bromide. For the other two bromo-compounds, requiring higher temperatures, equipment depicted as Figs. 1 and 2 by Le Fèvre, Ross, and Smythe was used, together with the oven and glass-diaphragm gauge mentioned by Freeman, Le Fèvre, and Maramba (*J.*, 1952, 1649). In all cases polarisations were estimated relatively to P_{CO_2} (taken as temperature invariant and equal to 7·341 c.c.; cf. Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374) *via* the equation:

$$P_{gas} = 7{\cdot}341\ (\delta C/p)^{gas}_{p=0}/(\delta C/p)^{CO_2}_{p=0}$$

Experimental procedures and methods of calculation were as described by Le Fèvre and Russell (*loc. cit.*). Essential observations are listed in Table 2.

Table 2. *Polarisation–temperature relations.*

T, °K	$(\delta C/p)^{gas}_{p=0}$	P, c.c. (obs.)	P, c.c. (calc.)	p, range in cm.	No. of obsns.	T, °K	$(\delta C/p)^{gas}_{p=0}$	P, c.c. (obs.)	P, c.c. (calc.)	p, range in cm.	No. of obsns.
					Methyl bromide *						
294·7	88·29	83·33	83·25	19—47	11	374·0	57·13	68·58	68·71	27—51	10
339·0	68·27	74·22	74·29	17—47	10	404·8	49·78	64·72	64·60	21—52	12
350·5	64·36	72·36	72·34	18—50	10	455·6	40·31	59·06	59·04	16—59	10
					Methylene dibromide †						
362·9	40·36	57·07	56·89	10—20	10	448·7	28·59	50·09	50·39	9—43	12
378·8	37·60	55·52	55·46	16—30	11	488·0	25·18	48·04	48·17	9—31	11
397·0	34·90	54·03	53·97	13—39	10	523·6	22·87	46·84	46·46	11—57	12
419·0	31·86	52·08	52·34	13—36	11						
					Bromoform †						
394·2	29·31	45·06	44·87	4—10	11	452·4	24·16	42·69	42·90	7—26	8
426·5	26·50	44·11	43·72	11—30	9	466·2	22·98	41·86	42·52	5—32	12
434·1	25·59	43·37	43·47	13—35	13	494·0	21·96	42·41	41·79	5—52	11
436·5	25·30	43·11	43·39	5—24	12	507·0	20·94	41·52	41·48	6—29	12

* Standardising equation: $(\delta C/p)^{CO_2}_{p=0} = (2307{\cdot}4/T) - 0{\cdot}054$.

† Standardising equation: $(\delta C/p)^{CO_2}_{p=0} = (1901/T) - 0{\cdot}047$.

In each of the three cases the observed polarisations (P, obs.) were fitted by the method of least squares to "Debye" equations of the form $P = A + B/T$; the figures under P, calc. have been computed from the constants A and B so obtained. If for a given set P, obs. $- P$, calc. $= \Delta$, then the standard errors in A and B may be estimated by the formulæ cited for this purpose by Harris, Le Fèvre, and Sullivan (*loc. cit.*). Thus our results appear as follows:

CH_3Br: $P = (14{\cdot}7 \pm 0{\cdot}4) + (20{,}205 \pm 113)/T$; $\mu_{gas} = 1{\cdot}821 \pm 0{\cdot}005$ D.
CH_2Br_2: $P = (22{\cdot}9 \pm 0{\cdot}8_4) + (12{,}330 \pm 352)/T$; $\mu_{gas} = 1{\cdot}42 \pm 0{\cdot}02$ D.
$CHBr_3$: $P = (29{\cdot}6 \pm 2{\cdot}0) + (6005 \pm 286)/T$; $\mu_{gas} = 0{\cdot}99 \pm 0{\cdot}2$ D.

In Table 3 these values are compared with those recorded previously.

Measurements on Solutions in Benzene.—These have been made at 25° by the usual procedures (Le Fèvre, "Dipole Moments," Methuen, 2nd Edn., 1948, pp. 31—42), the apparatus described by Le Fèvre and Ross (*J.*, 1950, 283) and by Calderbank and Le Fèvre (*J.*, 1948, 1949) being used. The methyl bromide was dissolved in benzene as was sulphur dioxide by Le Fèvre and Ross, and similar methods were adopted for transferring the solutions to the cell or pyknometer. Calculations and symbols used have been explained previously (Le Fèvre, *Trans. Faraday Soc.*, 1950, **46**, 1, and footnote to Buckingham and Le Fèvre, *J.*, 1952, 1932); however, in the case of methylene dibromide it seemed necessary to assume that both $\varepsilon_{12} - \varepsilon_1$ and

TABLE 3. *Comparison between present and previous measurements.*

μ (D)	Results as :	No. of temps. studied	Author(s) and ref.
		Methyl bromide	
1·82	$P = 14{\cdot}7 + 20{,}205/T$	6	Present work
1·82	—	—	(Calc. from Pohrt, *Ann. Physik*, 1913, **42**, 569, by Höjendahl, *Physikal. Z.*, 1929, **30**, 392)
1·79	Individual polarisations	5	Mahanti, *ibid.*, 1930, **31**, 546
1·78	$P = 15{\cdot}40 \pm 19{,}580/T$	5	Smyth and McAlpine, *J. Chem. Physics.*, 1934, **2**, 499
1·75	Individual polarisations	5	Mahanti, *Phil. Mag.*, 1935, **20**, 274
1·79	Individual polarisations	4	Groves and Sugden, *J.*, 1937, 158
$1{\cdot}79_7$	Stark splitting	—	Shulman, Dailey, and Townes, *Phys. Rev.*, 1950, **78**, 145
		Methylene dibromide	
1·42	$P = 22{\cdot}9 \pm 12{,}330/T$	7	Present work
1·43	$P = 23{\cdot}51 \pm 12{,}445/T$	5	Maryott, Hobbs, and Gross, *J. Amer. Chem. Soc.*, 1941, **63**, 659
		Bromoform	
0·99	$P = 29{\cdot}6 \pm 6005/T$	8	Present work

$d_{12} - d_1$ were represented by $aw_2 + bw_2^2$, and to obtain the " best possible " figures for a, *i.e.*, $(\alpha\varepsilon_1)_{w=0}$ and $(\beta d_1)_{w=0}$, by the method of least squares (cf. Harris, Le Fèvre, and Sullivan, *J.*, 1953, 1622). Table 4 sets out the measurements; the values of μ shown have been computed with the help of the distortion polarisations ascertained during the present work.

TABLE 4. *Dielectric constants and densities of solutions in benzene at 25°.*

10^5w_2	ε_{12}	$\alpha\varepsilon_1$	$(d_4^{25})_{12}$	β	10^5w_2	ε_{12}	$\alpha\varepsilon_1$	$(d_4^{25})_{12}$	β
0	2·2725	—	0·87378	—					
				Methyl bromide					
23,282	2·3387	2·84	0·88288	0·447	40,543	2·3839	2·75	0·88980	0·452
33,397	2·3655	2·78	0·88682	0·447	69,156	2·4624	2·89	0·90048	0·442
39,520	2·3819	2·77	0·88940	0·452	83,759	2·5008	2·73	0·90610	0·442
Whence mean $\alpha\varepsilon_1 = 2{\cdot}79$; mean $\beta = 0{\cdot}447$; $_\infty P_2 = 67{\cdot}7 \pm 1{\cdot}25$ c.c.; $\mu_{C_6H_6} = 1{\cdot}61 \pm 0{\cdot}03$ D.									
				Methylene bromide					
20,952	2·2999	1·322	0·88570	0·656	55,668	2·3461	1·322	0·90615	0·665
40,378	2·3256	1·315	0·89708	0·660	65,802	2·3590	1·335	0·91161	0·668
40,616	2·3260	1·317	0·89716	0·659	73,825	2·3724	1·349	0·91757	0·678
Whence $\alpha\varepsilon_1 = 1{\cdot}28_2 + 0{\cdot}85_6w_2$; $\beta = 0{\cdot}637 + 0{\cdot}539w_2$; $_\infty P_2 = 63{\cdot}4 \pm 0{\cdot}6$ c.c.; $\mu_{C_6H_6} = 1{\cdot}41 \pm 0{\cdot}02_5$ D.									
				Bromoform					
16,209	2·2812	0·537	0·88374	0·703	41,117	2·2949	0·549	0·89951	0·716
18,952	2·2827	0·538	0·88542	0·703	48,205	2·2988	0·546	0·90409	0·720
31,292	2·2891	0·531	0·89355	0·723	54,404	2·3016	0·535	0·90835	0·727
32,423	2·2898	0·534	0·89443	0·729	60,042	2·3048	0·538	0·91188	0·726
37,157	2·2922	0·530	0·89728	0·724	72,981	2·3121	0·543	0·92059	0·734
Whence mean $\alpha\varepsilon_1 = 0{\cdot}538$; $\beta = 0{\cdot}706 + 0{\cdot}366w_2$; $_\infty P_2 = 50{\cdot}91 \pm 0{\cdot}54$ c.c.; $\mu_{C_6H_6} = 1{\cdot}02 \pm 0{\cdot}06$ D.									

The moments now recorded are compared in Table 5 with others previously reported by Müller and Sack (*Physikal. Z.*, 1930, **31**, 815) and Le Fèvre and Russell (*J.*, 1936, 491).

TABLE 5. *Apparent moments in benzene.*

Solute	Temp.	No. of solns.	μ, D *	μ, D †	Authors
CH_3Br	25°	6	1·61	—	Present
CH_2Br_2	25	6	1·41	—	,,
	25	2	1·37	1·38 (21·5)	Müller and Sack
$CHBr_3$	25	10	1·02	—	Present
	25	4	1·02	0·99 (30·5)	Müller and Sack
	25	2	1·07	1·06 (30)	Le Fèvre and Russell

* Using the $_DP$ from measurements on gases.
† Using the molecular refractions shown in parentheses.

Discussion.—Table 6 contains the molecular constants and values of $\mu_{C_6H_6}/\mu_{gas}$ predicted by equations (1), (2), (3), and (4) of the paper of Buckingham and Le Fèvre (*loc. cit.*), the symbols being those defined and employed by these authors. The $(n^2)_D^{25}$ figures, other than that of benzene for which $(n^2)_D^{25} = 2{\cdot}2417$, have been calculated from Vogel's refractivities (*J.*, 1948, 1842) and the densities listed in Table 7. The ξ's were determined from the A's, B's, and C's by referring to Osborn's graphs (*Physical Rev.*, 1945, **67**, 351). When applying equation (4), *i.e.*, Ross and Sack's expression (*Proc. Phys. Soc.*, 1950, *B*, **63**, 893), $n^2_{eff.}$ values (from ${}_DP_2$ and d_2) of 2·044, 2·447, and 2·525 respectively were used; the datum for bromoform, in comparison with the value of $(n^2)_D^{25}$ for that compound, seems possibly a little low.

TABLE 6.

						$\mu_{C_6H_6}/\mu_{gas}$ calc. by equation:				
Substance	A	B	C	—	$(n^2)_D^{25}$	(1)	(2)	(3)	(4)	Ratio found
CH_3Br	5·54	3·80	3·80	0·24	2·015	0·92	0·92	0·91	0·90	$0{\cdot}88_5 \pm 0{\cdot}02$
CH_2Br_2	4·30	6·56	3·60	0·36	2·376	0·99	0·98	0·98	1·04	$0{\cdot}99 \pm 0{\cdot}03$
$CHBr_3$	6·30	6·86	6·86	0·36	2·544	1·13	1·11	1·07	1·05	$1{\cdot}03 \pm 0{\cdot}08$

From Table 6 it may be seen that each of the equations (1)—(4) predicts ratios which are essentially of the correct orders; nos. (2), (3), and (4) appear on the whole preferable to (1)—a conclusion already drawn by Buckingham and Le Fèvre (*loc. cit.*).

Calculation of μ_{gas} from Measurements on Pure Liquids.—The shape factors and values of $(n^2)_D^{25}$ of Table 6 being used in conjunction with appropriate ε's and d's from the literature, μ_{gas} has been estimated from $\mu_{liq.}$ *via* equations (5), (6), and (7) of Buckingham and Le Fèvre. Results are in Table 7, and it is evident that equations (5) and (6) are most satisfactory for these molecules, and superior to Onsager's equation (7).

TABLE 7. *Calculation of μ_{gas} from $\mu_{liq.}$*

				μ_{gas}, calc. by eqn.:			
Liquid	ε	d	$\mu_{liq.}$	(5)	(6)	(7)	μ_{gas}, found
CH_3Br	$9{\cdot}0_2$ [1]	1·668 [1]	1·14	1·84	1·84	1·63	1·82
CH_2Br_2	$7{\cdot}22_5$ [1, 2]	2·470 [3]	1·10	1·43	1·42	1·39	1·42
$CHBr_3$	4·398 [4]	2·878 [5]	0·91	0·97	0·98	1·01	0·99

[1] Extrapolated from Morgan and Lowry, *J. Phys. Chem.*, 1930, **34**, 2385. [2] Interpolated value from Smyth and Rogers, *J. Amer. Chem. Soc.*, 1930, **52**, 2227. [3] Perkin, *J.*, 1884, **45**, 520. [4] Le Fèvre and Le Fèvre, *J.*, 1935, 1747. [5] Sherman and Sherman, *J. Amer. Chem. Soc.*, 1928, **50**, 1119.

UNIVERSITY OF SYDNEY, N.S.W., AUSTRALIA. [*Received, May 20th*, 1953.]

---

688. *The Course of the Perkin Coumarin Synthesis. Part I.*

By MALCOLM CRAWFORD and J. A. M. SHAW.

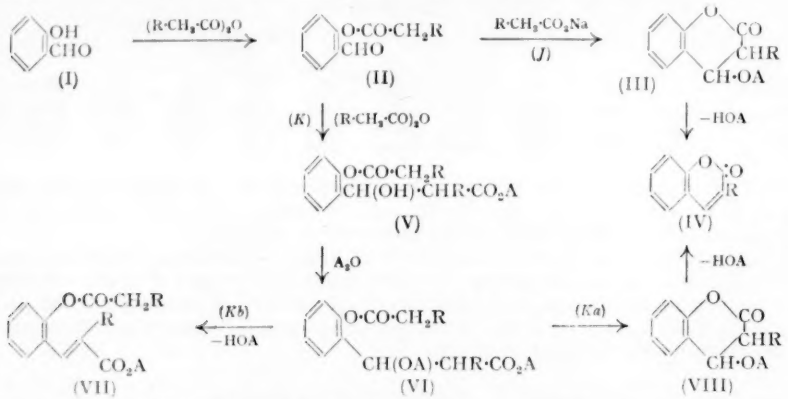
The condensation of salicylaldehyde and its derivatives with acid anhydrides and the corresponding sodium salts can take place both intramolecularly and intermolecularly to give the same coumarin, in the latter case frequently accompanied by the corresponding *o*-coumaric acid. A novel method of converting *o*-coumaric acid into coumarin in good yield is described.

IN the Perkin synthesis of coumarin from salicylaldehyde, acetic anhydride, and sodium acetate, *o*-hydroxycinnamic acid is unlikely to be an intermediate. Its *trans*-isomer, *o*-coumaric acid, does not lactonise under the conditions of the reaction. The *cis*-isomer, *o*-coumarinic acid, lactonises very readily, but the formation of *cis*-acids in the Perkin reaction is met with rarely and then only in small amount (cf., *e.g.*, Bakunin, *Gazzetta*, 1895, **25**, 137; Breslow and Hauser, *J. Amer. Chem. Soc.*, 1939, **61**, 786). The following scheme is now suggested as providing a satisfactory reaction mechanism. There are three distinct reaction sequences, all found to occur. As double-bond formation takes place last in each case, no stereochemical difficulties arise.

Course *J* (intramolecular condensation) consists of (*a*) acylation, (I) ⟶ (II), (*b*) intramolecular condensation, (II) ⟶ (III) (A = H or acyl), and (*c*) double-bond formation by elimination (III) ⟶ (IV).

Course *Ka* (intermolecular condensation) consists of (*a*) acylation, (I) ⟶ (II), (*b*) intermolecular condensation, (II) ⟶ (V), and further acylation, (V) ⟶ (VI) (A = acyl), (*c*) cyclisation (lactonisation), (VI) ⟶ (VIII), and (*d*) double-bond formation by elimination, (VIII) ⟶ (IV).

Course *Kb* (intermolecular condensation leading to the *trans*-acid) consists of (*a*) and (*b*) as in course *Ka*, then (*c*) double-bond formation by elimination, (VI) ⟶ (VII).

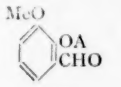


Intramolecular Condensation.—Course *J* is similar to that suggested by Heilbron, Hey, and Lythgoe (*J.*, 1936, 295) for the formation of 6-methoxy-4-methyl-3-phenylcoumarin from 2-hydroxy-4-methoxyacetophenone by the Kostanecki reaction using sodium phenylacetate and phenylacetic anhydride, except that an *o*-hydroxyarylaldehyde is substituted for an *o*-hydroxyaryl ketone. Salicylaldehyde reacts similarly with sodium phenylacetate and acetic anhydride to produce 3-phenylcoumarin. This is Oglialoro's modification (*Gazzetta*, 1878, **8**, 429) of the Perkin reaction. In it phenylacetic anhydride is the essential reactant. If acetylsalicylaldehyde (II; R = H) is used, 3-phenylcoumarin is formed in good yield in the absence of acetic anhydride. Trans-esterification, converting (II; R = H) into (II; R = Ph), occurs, as a mixture of acetylsalicylaldehyde, benzaldehyde, and sodium phenylacetate gives, on heating, 3-phenylcoumarin and not α-phenylcinnamic acid. Phenylacetylsalicylaldehyde (II; R = Ph), when heated with sodium acetate, or better phenylacetate, gives 3-phenylcoumarin in good yield, thus confirming the reaction sequence. Strong heating of phenylacetylsalicylaldehyde alone gives only very little 3-phenylcoumarin. When these esters are heated with sodium phenylacetate intermolecular condensation is excluded. The rather lower yields obtained indicate that in the presence of anhydride some intermolecular condensation occurs. This is substantiated by the high yield given when acetylsalicylaldehyde, acetic anhydride, and sodium phenylacetate are heated together.

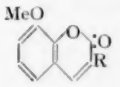
Intermolecular Condensation.—Intramolecular condensation does not occur in the reaction between salicylaldehyde, acetic anhydride, and sodium acetate, as acetylsalicylaldehyde gives not more than a trace of coumarin when heated with sodium acetate even on addition of various salts, bases, solvents, or dehydrating agents (see Experimental section). Acetic anhydride addition, however, leads to ready coumarin formation, although a mixture of benzoic anhydride and sodium benzoate is ineffective. The function of the acetic anhydride is, therefore, not merely that of solvent or dehydrating agent but of reactant. Since acylation is already complete the only alternative is for the anhydride to condense, leading to compounds (V) and (VI) (R = H, A = Ac). Two possibilities now appear: (*a*) cyclisation giving (VIII; R = H, A = Ac), followed by elimination and double-bond formation, yielding coumarin (IV; R = H); and (*b*) loss of acetic acid from

(VI), *i.e.*, elimination instead of cyclisation, to give (VII; R = H, A = Ac). This compound has the *trans*-configuration and has been formed by the normal Perkin reaction sequence. It cannot give rise to coumarin but yields instead a substituted cinnamic acid.

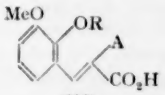
The Formation of trans-*Acid.*—*trans*-Acids are frequent by-products in coumarin syntheses. When the hydroxyl group of salicylaldehyde is methylated or replaced by almost any other group, including H, the *trans*-acid is the sole product because the cyclisation *Ka* cannot occur. The ordinary Perkin reaction is thus a special case (*Kb*) of a more general reaction which with appropriately substituted aldehydes can take three different courses, *J*, *Ka*, or *Kb*. 3-Methoxysalicylaldehyde (IX; A = H), in the coumarin synthesis, gives 8-methoxycoumarin (X; R = H) and a much larger amount of 2-acetoxy-3-methoxycinnamic acid (XI; R = H, A = Ac) according to Mauthner (*J. pr. Chem.*, 1939, **152**, 23) and Dey and Kutti (*Proc. Nat. Inst. Sci., India*, 1940, **6**, 641). This has been confirmed. With acetic anhydride and sodium phenylacetate the main product is 8-methoxy-3-phenylcoumarin (X; R = Ph) accompanied by some 2-acetoxy-3-methoxy-α-phenylcinnamic acid (XI; R = Ph, A = Ac), an acetyl derivative which on hydrolysis



(IX)



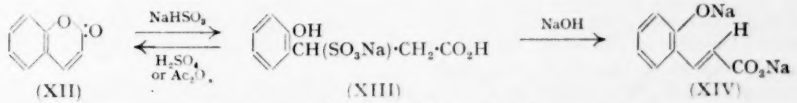
(X)



(XI)

gives the free hydroxy-acid (XI; R = Ph, A = H). The much lower yield of *trans*-acid is due to the predominance of intramolecular condensation. This is proved by heating 2-acetoxy-3-methoxybenzaldehyde (IX; A = Ac) with sodium phenylacetate in absence of anhydride. Only the coumarin is formed and no *trans*-acid, since intermolecular condensation is eliminated. All three reaction sequences thus occur in the condensation of 3-methoxysalicylaldehyde with phenylacetic anhydride. The appreciable yields of *trans*-acid in the condensations of this aldehyde are probably due to steric interference of the *o*-methoxy-group with cyclisation *Ka*. The alternative mechanism *Kb*, which is not affected, consequently supplants it.

Further Remarks on Intermolecular Condensation.—The following observations have some bearing on intermolecular condensation. When coumarin (XII) is heated with sodium sulphite or hydrogen sulphite solution a compound (XIII) is obtained (Dey and Row, *J.*, 1924, 554; Dodge, *J. Amer. Chem. Soc.*, 1916, **38**, 446), resembling the aldol intermediate in the Perkin reaction. Treated with sodium hydroxide solution (XIII) loses $NaHSO_3$ and gives (XIV). The action of sulphuric acid or acetic anhydride, however, on (XIII) causes cylisation first, and then elimination, to give coumarin (XII). As in stages *Ka* and *Kb* the *trans*-acid is formed if elimination is first, but coumarin if cyclisation precedes it.



(XII) (XIII) (XIV)

Heating *o*-coumaric acid with acetic anhydride and sodium acetate merely acetylates it. Tiemann and Herzfeld (*Ber.*, 1877, **10**, 283) heated the solid acetyl derivative above its melting point, causing decomposition with evolution of acetic acid and formation of coumarin. Thus isomerisation does take place under forced conditions. It has now been noted that *o*-coumaric acid, when heated with acetic anhydride or, better, butyric anhydride and a very little iodine readily gives coumarin in good yield. Iodine in acetic or butyric acid is ineffective. The reaction does not depend, therefore, on iodine addition, or on acylation since ethylcoumarin is not obtained when butyric anhydride is used. More probably the addition of some entity, acetylium iodide, iodine acetate, or an ion of one of these, gives a free-rotation phase, thus reversing stage *Kb*, so leading through ring closure *Ka* to coumarin.

Acetylsalicylaldehyde with butyric anhydride and sodium butyrate gives 3-ethyl-

coumarin, which is not conclusive proof of intermolecular condensation owing to the ease of trans-esterification, *e.g.*, acetylsalicylaldehyde with benzoic anhydride and sodium benzoate yields only benzoylsalicylaldehyde. Trans-esterification occurs, the liberated acetyl group passing into sodium acetate rather than acetic anhydride as no coumarin is formed.

The Yield of Coumarin.—The overall equation for the synthesis of coumarin is:

$$HO{\cdot}C_6H_4{\cdot}CHO + 2(CH_3{\cdot}CO)_2O = \text{Coumarin} + 3CH_3{\cdot}CO_2H$$

The quantities usually recommended (*e.g.*, Cohen, "Practical Organic Chemistry," Macmillan, London, 1924, p. 221) are one mol. of salicylaldehyde to 1·6 mol. of acetic anhydride. According to Yanagisawa and Kondô (*J. Pharm. Soc. Japan*, 1921, **472**, 498; *A*, 1921, i, 682) such quantities give a 27% yield. The optimum yield (45·8%) is now found to be obtained by using two mols. of the anhydride.

Experimental

Action of Acetic Anhydride and Sodium Acetate on o-Coumaric Acid.—*o*-Coumaric acid (4 g.) was heated with acetic anhydride (10 ml.) and sodium acetate (4 g.) for 6 hr. at 180°. The mixture was poured into sodium carbonate solution and extracted with ether. No coumarin was found in the ether but acidification of the carbonate solution gave a precipitate having, after crystallisation from aqueous alcohol, m. p. 145°, which is identical with that of *o*-acetoxycinnamic acid.

Perkin–Oglialoro Condensation of Salicylaldehyde.—Salicylaldehyde (5 g.), acetic anhydride (9 g.), and sodium phenylacetate (12 g.) were heated together for 2 hr. at 180°. The cooled product was warmed with water, cooled, and filtered off. The resulting yellow solid gave pale yellow needles (from alcohol) of 3-phenylcoumarin (6·3 g., 69%), m. p. 142°.

Action of Sodium Phenylacetate on Acetylsalicylaldehyde.—A mixture of the two substances (12 and 5 g. respectively) was heated for 2 hr. at 170°. The brown solid product on decolorisation and crystallisation from alcohol gave 3-phenylcoumarin (3·5 g., 52%), m. p. 141—142°.

Acetylsalicylaldehyde, Benzaldehyde, and Sodium Phenylacetate.—A mixture of the three substances (5, 8, and 12 g., respectively) was heated for 2 hr. at 170°. From the product benzaldehyde, phenylacetic acid, and 3-phenylcoumarin, but no α-phenylcinnamic acid, were recovered.

Phenylacetylsalicylaldehyde.—Phenylacetyl chloride (5 g.) was added to a suspension of the sodium salt of salicylaldehyde (4·5 g.) in dry ether (20 ml.) and the whole heated under reflux for 1 hr. Next morning the sodium chloride formed was filtered off. After removal of the ether the yellow oil remaining was distilled, giving a fraction, b. p. 130—170°/0·7 mm., which solidified. After washing of its ethereal solution with sodium carbonate the *phenylacetylsalicylaldehyde* was finally obtained as fine needles (from aqueous alcohol), m. p. 52°, having a pleasant odour (Found: C 74·2; H, 5·0. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%). The yield was poor. Its *semicarbazone* crystallised from alcohol in fine needles m. p. 176° (Found: C, 64·3; H, 5·4; N, 14·2. $C_{16}H_{15}O_3N_3$ requires C, 64·6; H, 5·1; N, 14·1%).

Action of Sodium Acetate on Phenylacetylsalicylaldehyde.—The two substances (0·2 g. each) were heated together at 170—180° for 2 hr., but did not become completely molten. 3-Phenylcoumarin (27%), m. p. 141—142°, was obtained.

Action of Sodium Phenylacetate on Phenylacetylsalicylaldehyde.—The two substances (0·6 and 0·3 g. respectively) were heated similarly; the mixture melted completely. The yield of 3-phenylcoumarin was 53·5%.

Action of Heat on Phenylacetylsalicylaldehyde.—Phenylacetylsalicylaldehyde (0·2 g.) was heated at 210—220° for 2 hr. The product was dissolved in hot alcohol, which on cooling deposited a small amount (>0·02 g.) of 3-phenylcoumarin, m. p. 141—142°.

Action of Acetic Anhydride and Sodium Acetate on 3-Methoxysalicylaldehyde.—The three substances (30, 15, and 10 g., respectively) were heated at 180° for 6 hr. The product was shaken with sodium hydroxide solution and extracted with ether. From the ethereal extract was obtained 8-methoxycoumarin (1·2 g., 10·5%), m. p. 87—89° (from water). Acidification of the alkaline layer gave 2-hydroxy-3-methoxycinnamic acid (3·1 g., 24%), m. p. 175—176° (from aqueous alcohol).

Perkin–Oglialoro Condensation of 3-Methoxysalicylaldehyde.—3-Methoxysalicylaldehyde (10 g.) acetic anhydride (25 g.), and sodium phenylacetate (25 g.) were heated at 180° for 6 hr. The

product was treated with sodium carbonate solution. The insoluble portion on recrystallisation from alcohol gave *8-methoxy-3-phenylcoumarin* (8·1 g., 51%), pale yellow needles, m. p. 162° (Found: C, 75·9; H, 4·8. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·8%). The alkaline filtrate on acidification gave a mixture of acids which was extracted with hot water to remove phenylacetic acid. The residue separated from alcohol in colourless needles, m. p. 225°, of *2-acetoxy-3-methoxy-α-phenylcinnamic acid* (1·1 g., 5·3%) (Found: C, 69·5; H, 5·1. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2%). A portion of this acid was hydrolysed by hot 10% sodium hydroxide solution for 5 hr. *2-Hydroxy-3-methoxy-α-phenylcinnamic acid* was obtained as colourless needles, m. p. 198°, from aqueous alcohol (Found: C, 71·5; H, 5·3. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2%).

Action of Sodium Phenylacetate on 2-Acetoxy-3-methoxybenzaldehyde.—The two substances (8 and 5 g. respectively) were heated together for 2 hr. at 180°. The aqueous extract of the product on acidification gave only phenylacetic acid. The aqueous sodium carbonate extract of the residue on acidification gave no precipitate. The residue separated from alcohol in long pale yellow needles of 8-methoxy-3-phenylcoumarin, m. p. 162° (2·6 g., 40%).

Action of Acetic Anhydride and Sodium Phenylacetate on Acetylsalicylaldehyde.—The three reactants (6·5 g., 12 g. and 5 g. respectively) were heated at 170° for 2 hr. The product was poured into warm water, cooled and filtered. The residue, crystallised from alcohol, gave 3-phenylcoumarin, m. p. 141—142° (4·5 g., 66·5%).

Attempts to Convert Acetylsalicylaldehyde into Coumarin without Use of Acetic Anhydride.—Acetylsalicylaldehyde (4 g.) was heated at 180° or under reflux for 2—5 hr. as follows: (1) with sodium acetate (4 g.), (2) with potassium acetate and formate (5 g. each), (3) with pyridine (10 ml.) and a trace of piperidine, (4) with sodium acetate (4 g.), acetic acid (4 g.), and pyridine (excess), (5) with sodium acetate (4 g.) and xylene (50 ml.) in a Dean and Stark flask (no water was formed), (6) with sodium acetate (4 g.) and quinoline (10 ml.), (7) with sodium acetate (4 g.) and acetamide (10 g.), (8) with sodium acetate (4 g.) and pyridine (10 ml.), (9) with sodium acetate (4 g.) and ethylene glycol (10 ml.), (10) with sodium acetate (4 g.) and acetic acid (excess) which was allowed to distil over during the heating, and (11) with zinc chloride (2 g.). The reaction product in each case was poured into water, and the mixture extracted with ether. In no instance was more than a trace of coumarin obtained.

Action of Benzoic Anhydride and Sodium Benzoate on Acetylsalicylaldehyde.—The three reactants (14, 8, and 5 g., respectively) were heated at 180° for 4 hr. and the product poured into warm water. An ethereal extract, when washed with sodium carbonate solution and evaporated, yielded an oil. This was benzoylsalicylaldehyde and gave benzoic acid on hydrolysis.

Action of Butyric Anhydride and Sodium Butyrate on Acetylsalicylaldehyde.—The three reactants (20, 13·5, and 10 g., respectively) were heated for 2 hr. at 180°. An ethereal extract of the product was washed, dried, and distilled, finally under reduced pressure, giving an oil (b. p. 160°/14 mm.) which solidified to crystals of 3-ethylcoumarin (2·85 g., 26%), m. p. 74°, which depressed the m. p. of coumarin.

Conversion of o-Coumaric Acid into Coumarin.—A mixture of *o*-coumaric acid (5 g.), iodine (0·1 g.), and acetic anhydride (10 ml.) was heated at 180° for 2 hr. The product was poured into warm water. An ethereal extract was washed with sodium carbonate solution and dried, and the ether removed. The residue on crystallisation from light petroleum (b. p. 60—80°) gave coumarin (2·4 g., 54·5%).

Similarly, *o*-coumaric acid (4 g.), iodine (0·1 g.), and butyric anhydride (15 ml.) yielded a product (2·1 g., 60%) which did not depress the m. p. of a sample of coumarin.

When the anhydride was replaced by acetic acid (15 ml.) or butyric acid (15 ml.), only unchanged *o*-coumaric acid was recovered.

Effect of the Proportion of Acetic Anhydride on the Yield of Coumarin.—Salicylaldehyde (10 g., 1 mol.), sodium acetate (2·5 mols.), and acetic anhydride (8·36—25·08 g., 1—3 mol.) were heated for 5 hr. at 180°. The product was poured into warm water. An ethereal extract was shaken with sodium hydrogen sulphite solution, washed, and dried, and the ether removed. The resulting solid was dissolved in alkali, and the solution was boiled with charcoal, filtered, and acidified. The precipitated coumarin was crystallised from light petroleum (60—80°), yields being:

Ac_2O (mol.)	1	2	3
Yield (%)	19	45·8	40

College of Technology, Belfast.

[*Received, June 1st*, 1953.]

689. *Indoles. Part IV.* Synthetical Applications of the Oxidative Fission of the $C_{(2)}$–$C_{(3)}$ Bond in Indoles.*

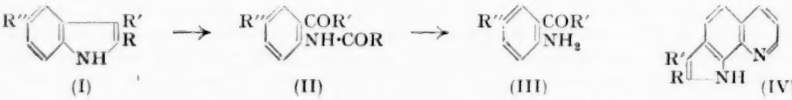
By D. W. Ockenden and K. Schofield.

Suitably substituted indoles were converted into 2-*o*-benzamidobenzoylpyridine and into 2-acetamidophenyl benzyl ketone and its 5-methyl- and 5-nitro-analogues. These derivatives were hydrolysed to the corresponding amines.

4′ : 5′-Dimethylpyrrolo(3′ : 2′-7 : 8)quinoline gave by the same method 8-acetamido-7-acetylquinoline, from which were obtained 7-acetyl-8-amino- and 8-amino-7-ethyl-quinoline.

Earlier work has been concerned with aspects of oxidative fission of the indole $C_{(2)}$–$C_{(3)}$ bond (I ⟶ II). We now describe applications of this type of reaction to the synthesis of 2-aminoaryl ketones (III).

(*a*) Hitherto 2-*o*-aminobenzoylpyridine (III; R′ = 2-C_5H_4N, R″ = H) has been prepared by a tedious many-staged process (Nunn and Schofield, *J.*, 1952, 583). Oxidation of a suitable 3-2′-pyridylindole promised to make the compound more readily available. No 3-2′-pyridylindole has been described. Accordingly, the readily available 2-phenacyl-



pyridine (Goldberg, Barkley, and Levine, *J. Amer. Chem. Soc.*, 1951, **73**, 4301) was converted into its phenyl- (*idem, ibid.*), *p*-tolyl-, and *p*-nitrophenyl-hydrazone. The first two were readily cyclised in high yield by hydrochloric acid to 2-phenyl- (I; R = Ph, R′ = 2-C_5H_4N, R″ = H) and 5-methyl-2-phenyl-3-2′-pyridylindole (I; R = Ph, R′ = 2-C_5H_4N, R″ = Me), but all attempts to cyclise the nitro-compound failed. The yield of 2-phenyl-3-2′-pyridylindole produced by boron trifluoride in acetic acid was lower, probably because of co-ordination of the reagent with the pyridyl group, and similar complications in the other cases are mentioned in the Experimental section.

Treatment of 2-phenyl-3-2′-pyridylindole in ethyl acetate with a large excess of ozone gave a good yield of 2-*o*-benzamidobenzoylpyridine, which was readily hydrolysed to 2-*o*-aminobenzoylpyridine. The method makes this amine easily available on the 10-g. scale, and is potentially of wider application than the earlier process.

(*b*) *o*-Aminophenyl benzyl ketone (III; R′ = CH_2Ph, R″ = H) has not been obtained before. The nitration of benzyl phenyl ketone (List, *Ber.*, 1893, **26**, 2452) is not useful in this connection, and earlier attempts at synthesis (Ruggli, Caspar, and Hegedus, *Helv. Chim. Acta*, 1937, **20**, 250; Lothrop and Goodwin, *J. Amer. Chem. Soc.*, 1943, **65**, 363) failed.

3-Benzyl-2-methylindole was obtained in unstated yield from a Fischer reaction by Kuroda (*J. Pharm. Soc. Japan*, 1923, **493**, 131), and by use of cuprous chloride as catalyst Janetsky and Verkade (*Rec. Trav. chim.*, 1945, **64**, 129) isolated the compound in 40% yield. We found zinc chloride to be a better catalyst, and boron trifluoride improved the yield further. By the Fischer reaction we also prepared 3-benzyl-2 : 5-dimethyl-, 3-benzyl-2-methyl-5-nitro-, and 3-benzyl-2-methyl-7-nitro-indole, and 2-methyl-3-(1′-naphthylmethyl)indole.

No crystalline product was isolated from the chromic acid oxidation of 3-benzyl-2-methylindole, a result expected in view of the absence of an electronegative substituent. Small yields of unidentified products were isolated from the 5- and the 7-nitro-compound. However, ozonisation and subsequent hydrolysis gave moderate yields of *o*-aminophenyl benzyl, 2-amino-5-methylphenyl benzyl, 2-amino-5-nitrophenyl benzyl, and *o*-amino-

* Part III, *J.*, 1953, 612.

phenyl 1-naphthylmethyl ketone, from the appropriate indoles. The diazotisation of these amines has been described by Ockenden and Schofield (*J.*, 1953, in the press).

(*c*) To identify the compound obtained by nitrating 7-ethylquinoline and reducing the product (Long and Schofield, *J.*, 1953, 2350), we required to synthesise 8-amino-7-ethylquinoline unambiguously. For this purpose ethyl methyl ketone 8-quinolylhydrazone was converted unto 4′ : 5′-dimethylpyrrolo(3′ : 2′-7 : 8)quinoline (IV; R = R′ = Me). The latter was converted by ozone into 8-acetamido-7-acetylquinoline. Catalytic reduction of this compound in acetic acid, in the presence of palladium–barium sulphate and perchloric acid (Long and Schofield, *loc. cit.*) gave 8-acetamido-7-ethylquinoline. Hydrolysis completed the orientation. No homogeneous product could be obtained by ozonisation of 4′-ethyl-5′-methylpyrrolo(3′ : 2′-7 : 8)quinoline (IV; R = Me, R′ = Et).

Experimental

(*a*) *Preparation of* 2-o-*Aminobenzoylpyridine.—Arylhydrazones.* Usually the ketone and arylhydrazine were heated in equivalent amounts at 95° for 1 hr. With examples which are not described further the resulting oil was dried (Na_2SO_4) in ether and used directly. Methyl phenethyl ketone *p*-(65%), m. p. 111—112°, and *o*-nitrophenylhydrazone (74%), m. p. 85—86°, formed copper-coloured and reddish-brown needles, respectively, from alcohol; these decomposed after a while. 2-*Phenacylpyridine* p-*nitrophenylhydrazone* (obtained from the components at 135° for ¾ hr.) formed dark orange leaflets, m. p. 147—149° (Found: C, 68·4; H, 5·3. $C_{19}H_{16}O_2N_4$ requires C, 68·7; H, 4·9%), from alcohol.

2-*Phenyl*-3-2′-*pyridylindole.* 2-Phenacylpyridine phenylhydrazone (11·5 g.) (Goldberg, Barkley, and Levine, *loc. cit.*) and concentrated hydrochloric acid (200 c.c.) were refluxed for 3 hr. Most of the solvent was removed and the solution was basified at 0° with ammonia solution. Crystallisation from aqueous alcohol gave 2-*phenyl*-3-2′-*pyridylindole* (7·9 g.), needles, m. p. 201—202° (Found: C, 84·6; H, 5·0; N, 10·3. $C_{19}H_{14}N_2$ requires C, 84·4; H, 5·2; N, 10·4%). By this method 26·3 g. of 2-phenacylpyridine gave 24·0 g. of product.

The hydrazone (0·87 g.), acetic acid (10 c.c.), and boron trifluoride etherate (0·46 g.), when refluxed for 3 hr., gave the indole (0·42 g.; m. p. 196—199°).

5-*Methyl*-2-*phenyl*-3-2′-*pyridylindole.* Phenacylpyridine *p*-tolylhydrazone (1·0 g.) and concentrated hydrochloric acid (20 c.c.) were refluxed for 3 hr. Isolated as above, the product formed fawn needles (from aqueous alcohol) of 5-*methyl*-2-*phenyl*-3-2′-*pyridylindole* (0·61 g.), m. p. 194—196° (Found: C, 84·0; H, 5·6. $C_{20}H_{16}N_2$ requires C, 84·5; H, 5·7%).

When the hydrazone (1·57 g.), acetic acid (16 c.c.), and boron trifluoride etherate (0·79 g.) were refluxed for 3 hr., and the solution was filtered and concentrated, a dark oil resulted. Crystallisation from aqueous alcohol gave a mixture of fawn needles and yellow prisms. The former (0·34 g.) were removed with benzene and were identical with the above indole. The yellow prisms [0·55 g.; m. p. 160—170° (decomp.)] were identical with material obtained by refluxing the indole with boron trifluoride in acetic acid.

After phenacylpyridine *p*-nitrophenylhydrazone had been refluxed with boron trifluoride in acetic acid for 4 days, removal of the solvent and passage of the product in benzene through alumina gave small pale yellow needles, m. p. 150—151°. The same compound was obtained by similar treatment of phenacylpyridine. The nitro-hydrazone could not be converted into an indole.

2-o-*Aminobenzoylpyridine.* 2-Phenyl-3-2′-pyridylindole (8·0 g.) in ethyl acetate (400 c.c.) was treated at room temperature with 3 equivalents of approximately 5%-ozonised oxygen (8 hr.). Removal of the solvent and crystallisation from aqueous ethanol of the oily product from three such experiments gave material (18·6 g.; m. p. 111—113°) pure enough for the next step. 2-o-*Benzamidobenzoylpyridine* formed leaflets, m. p. 113—114° (Found: C, 75·7; H, 4·6. $C_{19}H_{14}O_2N_2$ requires C, 75·5; H, 4·7%).

The benzamido-compound (18·6 g.) and concentrated hydrochloric acid (200 c.c.) were refluxed for 24 hr. Concentration, basification, and crystallisation of the product from methanol gave the desired amine (10·0 g.; m. p. 141—143°). The pure substance formed long, golden blades, m. p. 143—145° (Found: C, 72·5; H, 5·3. Calc. for $C_{12}H_{10}ON_2$: C, 72·7; H, 5·1%) alone and mixed with an authentic specimen (Nunn and Schofield, *loc. cit.*).

(*b*) *Preparation of* o-*Aminophenyl Ketones.—*3-*Benzyl*-2-*methylindole.* Methyl phenethyl ketone phenylhydrazone (8·0 g.; b. p. 180—184°/2 mm.), acetic acid (80 c.c.), and boron trifluoride etherate (5·0 g.) were refluxed for 6 hr. The hot solution was filtered and concen-

trated; crystallisation of the residue from methanol gave the indole (4·95 g., m. p. 118—119°). Alternatively, the hydrazone (9·6 g.) and powdered zinc chloride (6·6 g.) were heated gently until the mildly exothermic reaction began. The product was isolated by steam-distillation, extraction of the residue with ether, and crystallisation from methanol. 3-Benzyl-2-methylindole (4·9 g.) formed glistening needles, m. p. 119—120° (Found: C, 85·9; H, 6·6. Calc. for $C_{16}H_{15}N$: C, 86·8; H, 6·8%).

3-Benzyl-2 : 5-dimethylindole. The tolylhydrazone (8·5 g.), acetic acid (85 c.c.), and boron trifluoride etherate (5·1 g.) were refluxed for 6 hr. Filtration, concentration, and recrystallisation from methanol gave the *indole* (57%) as crisp flakes, m. p. 114—116° (Found: C, 87·0; H, 7·3. $C_{17}H_{17}N$ requires C, 86·8; H, 7·3%).

3-Benzyl-2-methyl-5-nitroindole. Methyl phenethyl ketone *p*-nitrophenylhydrazone (6·5 g.) and concentrated hydrochloric acid (65 c.c.) were heated at 95° for 5 hr. The product was crystallised from methanol (yield, 3·55 g.). *3-Benzyl-2-methyl-5-nitroindole* formed yellow leaflets, m. p. 160—161° (Found: C, 71·7; H, 5·05. $C_{15}H_{14}O_2N_2$ requires C, 72·1; H, 5·3%). The hydrazone (6·5 g.), acetic acid (65 c.c.), and boron trifluoride etherate (3·4 g.) when refluxed for 6 hr. gave, after one crystallisation from methanol, 50% of the indole, m. p. 159—160°.

3-Benzyl-2-methyl-7-nitroindole. Methyl phenethyl ketone *o*-nitrophenylhydrazone (7·8 g.) gave *3-benzyl-2-methyl-7-nitroindole* (2·5 g.), which formed orange needles, m. p. 137—138° (Found: C, 71·8; H, 5·0%), from methanol.

2-Methyl-3-1′-naphthylmethylindole. The appropriate hydrazone (10·5 g.), acetic acid (100 c.c.), and boron trifluoride etherate (5·3 g.) were refluxed for 3 hr. After filtration and removal of the solvent the dark oily product was passed in benzene through alumina. Addition of light petroleum (b. p. 60—80°) to the concentrated eluate gave *2-methyl-3-1′-naphthylmethylindole* (4·95 g.), which separated from benzene–light petroleum as prisms, m. p. 147—149° (Found: C, 88·9; H, 6·2. $C_{20}H_{17}N$ requires C, 88·5; H, 6·3%).

o-Aminophenyl benzyl ketone and related compounds. The relevant indole (0·5 g.) was treated with the theoretical amount of 5%-ozonised oxygen. Experiments in ethyl acetate (25 c.c.) were at 0°, and the products were isolated by concentration at room temperature. With acetic acid (25 c.c.) as solvent the products were isolated by basification and extraction with ether. The acetamido-compounds were hydrolysed by refluxing aqueous alcoholic hydrochloric acid for 3 hr. Concentration, basification, and recrystallisation of the precipitate gave the amine.

1. R = Ph, R′ = H 2. R = Ph, R′ = Me
3. R = Ph, R′ = NO_2 4. R = α-$C_{10}H_7$, R′ = H

Acetamido-ketone	Yield, %, in EtOAc	Yield, %, in AcOH	Form	M. p.	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
1	40	60 [1]	Yellow needles [2]	97—98°	$C_{18}H_{15}O_2N$	75·5	6·1	75·9	6·0
2	35	35	Needles [2]	81—83	$C_{17}H_{17}O_2N$	77·4	6·5	76·4	6·4
3	45	45	Yellow prisms [3]	174—175	$C_{16}H_{14}O_4N_2$	64·3	4·9	64·4	4·7
4	—	47 [1]	Fawn plates [2]	148—149	$C_{20}H_{17}O_2N$	78·0	5·8	79·2	5·7

[1] The same yields were obtained from 2 g. of the indole. [2] From ether–light petroleum (b. p. 60—80°). [3] From aqueous ethanol.

Amino-ketone, as	Acet-amide, g.	HCl, c.c.*	Yield of amine, %	Form	M. p.	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
1	4·2	50	83	Leaflets [1]	103—104°	$C_{14}H_{13}ON$	79·6	6·2	79·6	6·2
2	0·43	5	80	Fawn plates [2]	104—106	$C_{15}H_{15}ON$	80·2	6·8	80·0	6·7
3	0·8	10	74	Golden needles [2]	163—165	$C_{14}H_{12}O_3N_2$	65·3	4·9	65·6	4·9
4	1·55	15	75	Blades [2]	133—135	$C_{18}H_{15}ON,\frac{1}{4}H_2O$	81·6	6·0	81·3	5·9

* Volume of concentrated acid taken, together with an equal volume of water and 2 volumes of alcohol, except for the hydrolysis of 4, when 3 volumes of alcohol were taken.
[1] From light petroleum (b. p. 60—80°). [2] From ethanol.

(*c*) *Synthesis of* 8-*Amino-7-ethylquinoline.*—*4′ : 5′-Dimethylpyrrolo*(*3′ : 2′-7 : 8*)*quinoline.* Ethyl methyl ketone 8-quinolylhydrazone (5·0 g.), concentrated hydrochloric acid (80 c.c.), and acetic acid (80 c.c.) were refluxed for 3 hr. Most of the solvent was removed and the solution was basified. The *pyrroloquinoline* (73%) formed lemon-coloured plates, m. p. 156—158°, from ethanol (Found: C, 79·1; H, 6·0. $C_{13}H_{12}N_2$ requires C, 79·5; H, 6·2%).

4′-Ethyl-5′-methylpyrrolo(*3′ : 2′-7 : 8*)*quinoline.* Methyl *n*-propyl ketone 8-quinolylhydrazone (2·9 g.), concentrated hydrochloric acid, and acetic acid (50 c.c. of each) similarly gave the *4′-ethyl-5′-methyl* compound (70%), which formed yellow plates, m. p. 123—125° (Found: C, 79·8;

H, 6·9. $C_{14}H_{14}N_2$ requires C, 80·0; H, 6·7%), from light petroleum (b. p. 60—80°) containing a trace of benzene.

7-Acetyl-8-aminoquinoline. The dimethylpyrroloquinoline (0·5 g.) in ethyl acetate (25 c.c.) was treated with the theoretical amount of ozonised oxygen. Removal of the solvent and crystallisation of the oily residue from benzene–light petroleum (b. p. 60—80°) gave the desired product (0·13 g.). Use of acetic acid gave a slightly better yield (0·2 g.). *8-Acetamido-7-acetylquinoline* formed pale yellow needles, m. p. 157—158·5° (Found: C, 68·9; H, 5·4. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3%).

The acetamido-compound (0·6 g.), water (10 c.c.), and hydrochloric acid (10 c.c.) were refluxed for 2 hr. Basification of the solution and crystallisation of the product from light petroleum (b.p. 60—80°) containing a trace of benzene gave yellow crystals of *7-acetyl-8-aminoquinoline*, m. p. 107—109° (Found: C, 70·8; H, 5·3. $C_{11}H_{10}ON_2$ requires C, 70·9; H, 5·4%).

8-Amino-7-ethylquinoline picrate. 8-Acetamido-7-acetylquinoline (0·4 g.), when shaken with acetic acid (25 c.c.), perchloric acid (2 c.c.), and palladium–barium sulphate (0·4 g.) at 90° absorbed the correct amount of hydrogen in 2 hr. Filtration, concentration, and basification provided an oil which was refluxed with 6N-hydrochloric acid (35 c.c.). Basification and ether extraction gave an oil (0·2 g.), which with picric acid (0·28 g.) in methanol (5 c.c.) provided pure 8-amino-7-ethylquinoline picrate, m. p. 203—204° (decomp.) alone and mixed with a specimen prepared according to Long and Schofield (*loc. cit.*).

We are indebted to Imperial Chemical Industries Limited and the Council of University College, Exeter, for financial support, and to D.S.I.R. for a maintenance grant to one of us (D. W. O.).

WASHINGTON SINGER LABORATORIES,
PRINCE OF WALES ROAD, EXETER.

[*Received, June 11th,* 1953.]

---

690. *Rates of Ionization of* ·O–H *and* :N–H *Bonds.*

By R. P. BELL and R. G. PEARSON.

It has been shown that the reaction of hydrogen ions with the anions of *p*-nitrophenol and 2 : 6-dinitrophenol reaches equilibrium in less than one millisecond, thus disproving earlier reports of a slow reaction. The reaction of ethylenedinitramine with aqueous ammonia has been studied by a flow method and shows a measurable rate during a few milliseconds. Ethylenedinitramine has also been investigated as a catalyst in the dehydration of acetaldehyde hydrate; it has an abnormally low catalytic power, thus resembling the nitroparaffins and other pseudo-acids. It is concluded that proton transfers to or from oxygen and nitrogen atoms will normally be too fast for direct observation.

RECORDED examples of proton transfers which take place at a measurable rate are confined almost entirely to reactions involving a carbon–hydrogen bond, and it is generally considered that the transfer of a proton to or from an oxygen atom takes place too rapidly to be directly observed. There is however a report (Branch and Jaxon-Deelman, *J. Amer. Chem. Soc.*, 1927, **49**, 1765) that the ion of *p*-nitrophenol reacts at a measurable rate with hydrogen ions; the reaction was followed by conductivity measurements in 50% aqueous methanol, and with concentrations of about 0·005M half-times of several minutes were observed at −10°. A measurable rate seems not impossible for this type of proton transfer, since the anion and the acid differ considerably in charge distribution (cf. Bell, *J. Phys. Chem.*, 1951, **55**, 885), and the initial object of this work was to obtain further kinetic data with nitrophenols, by using modern methods for following fast reactions.

The first method employed was the thermal one developed by Bell and Clunie (*Proc. Roy. Soc.*, 1952, *A*, **212**, 16) which is suitable for the quantitative study of reactions with half-times down to about 3 seconds. The ions of *p*-nitrophenol and of 2 : 6-dinitrophenol were allowed to react with solutions of hydrochloric acid or with buffer solutions prepared from acetic or dichloroacetic acid. Concentrations were about 0·01M, and experiments were carried out at 0° and 25° in water and in 50% aqueous methanol. In every case the

reaction was too fast to enable any estimate of its velocity to be made, which means that it must have been effectively complete in less than one second.

Similar results were obtained when the range of measurement was extended by using a flow method, in which the pH of the solution is determined spectrophotometrically very soon after mixing.* When the anions of *p*-nitrophenol and 2 : 6-dinitrophenol reacted at room temperature with hydrochloric acid, reaction was complete in less than one millisecond. These results are in direct conflict with Branch and Jaxon-Deelman's observations (*loc. cit.*), and agree with the usual view that proton transfers to and from oxygen atoms are extremely fast.

It seemed more probable that measurable rates could be obtained for proton-transfers to or from nitrogen atoms, and the acidic system chosen for study was $\cdot NH\cdot NO_2$. The decomposition of nitramine probably has a rate-determining step involving the removal of a proton from the nitrogen of $HN{:}\overset{+}{N}\!<\!\begin{matrix}O^-\\OH\end{matrix}$ (cf. Pedersen, *J. Phys. Chem.*, 1934, **38**, 581; Bell and Trotman-Dickenson, *J.*, 1949, 1288), and the simple nitroparaffins have a much lower rate of ionization than any other compounds containing a CH group of measurable acidity. Measurements were carried out on the reaction of ethylenedinitramine with aqueous ammonia: this reaction goes almost to completion, since the nitramine has $pK_1 = 5{\cdot}35$, $pK_2 = 6{\cdot}66$ (Lindley and Speakman, *J.*, 1949, 1657).

A sample of ethylenedinitramine was kindly given to us by Dr. A. H. Lamberton (Sheffield University) and was recrystallised from water. Its reaction with ammonia proved too fast to observe by the thermal method, but a measurable rate was recorded by using the flow method, with bromophenol-blue as indicator. (Independent experiments show that the response of this indicator to changes in acidity is effectively instantaneous.) By using 0·02M-ethylenedinitramine and 0·03M-ammonia solution at room temperature a pH change of 0·21 units was recorded in the time interval 0·7—4 milliseconds. This corresponds to the second stage of the reaction, *i.e.* if the nitramine is written as AH_2, the rate-determining process may be either or both of the two following reactions:

$$HA^- + NH_3 \longrightarrow A^= + NH_4^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1a)$$

$$HA^- + OH^- \longrightarrow A^= + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1b)$$

In any case the integration of the rate equation gives

$$\log\{[NH_3] - [NH_3]_\infty\} = -0{\cdot}01kt + \text{constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where $[NH_3]_\infty$ is the equilibrium ammonia concentration. This assumes that the equilibrium between NH_3 and NH_4^+ is effectively instantaneous, and also that the concentration of HA^- is almost constant at 0·01M: the latter assumption is valid for the part of the reaction studied. k is strictly speaking a composite constant involving both the forward and reverse constants of reactions (1*a*) and (1*b*), but the reverse reactions can be neglected under our experimental conditions. In the pH range observed ($\simeq$7) almost all the ammonia present is in the form of NH_4^+, so that $[NH_3]$ is inversely proportional to $[H^+]$. The values of $[H^+]$ in the time interval 0·7—4 milliseconds can be estimated from the photographic record of the light absorption, and a plot of $\log\left\{\frac{1}{[H^+]} - \frac{1}{[H^+]_\infty}\right\}$ against time gives a straight line of slope $-0{\cdot}01k$.

The value thus obtained is $k = 1{\cdot}5 \times 10^5$ l./mole-sec., which may be compared with the value of about 0·007 l./mole-sec. obtained for the same composite constant in the reaction of nitroethane ($pK \simeq 9$) with aqueous ammonia (Pearson, *J. Amer. Chem. Soc.*, 1948, **70**, 204). If reaction (1*a*) is the rate-determining step, k is the second-order velocity constant for the reaction between HA^- and NH_3, but if the data are interpreted in terms of reaction (1*b*) as the rate-determining reaction the velocity constant for the reaction between AH^- and OH^- is about 10^8 l./mole-sec. This seems improbably high for a reaction between two ions of like charge, and we may conclude that reaction (1*a*) is more probable.

* The apparatus used resembled that of Dubois (*J. Biol. Chem.*, 1941, **137**, 123) and its construction will shortly be described by E. F. Caldin and F. W. Trowse. The measurements were made for us in the Chemistry Department of Manchester University by Dr. F. W. Trowse, to whom our best thanks are due.

The measurable rate of reaction of ethylenedinitramine with ammonia should be paralleled by a low activity as an acid catalyst. A convenient reaction for investigating this point is the dehydration of acetaldehyde hydrate, previously investigated by Bell and Higginson (*Proc. Roy. Soc.*, 1949, *A*, **198**, 141). These workers found that a large number of carboxylic acids and phenols (including nitrophenols) obeyed the relation

$$\log_{10} k_c/p = 0{\cdot}54 \log_{10} (qK_A/p) + 3{\cdot}75 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where k_c is the catalytic constant of the acid (in $\log_{10}$, min.$^{-1}$, l., moles^{-1}), K_A its dissociation constant in water, and p and q statistical factors, while a number of pseudo-acids, such as benzoylacetone and the nitroparaffins, gave catalytic constants 1 or 2 powers of ten lower than those predicted by equation (3). Experiments were therefore carried out with ethylenedinitramine as a catalyst for the above reaction, using the same procedure as Bell and Higginson (*loc. cit.*); the results are given in the Table.

Dehydration of acetaldehyde hydrate at 25° catalysed by ethylenedinitramine.

[Catalyst]	[$CH_3 \cdot CO_2H$]	k	k_c
0·0099	0·00033	0·0142	0·76
0·0149	0·00033	0·0174	0·73
0·0149	0·00245	0·0610	0·80
0·0161	0·00145	0·0371	0·50
0·0224	0·00245	0·0646	0·70
		Mean	0·70

All the solutions contained some acetic acid (formed by oxidation of acetaldehyde), the catalytic effect of which was allowed for in calculating k_c. The value calculated from equation (3), the first dissociation constant of the nitramine being used, is $k_c = 10$, so that the observed value is low by a factor of 14. This effect resembles that found by Bell and Higginson for the nitroparaffins, and justifies the describing of the nitramine as a pseudo-acid.

In view of the above results it seems likely that proton transfers to or from oxygen or nitrogen atoms can only be observed directly either by using special techniques for very fast reactions, or by using isotope-exchange methods for reactions which are thermodynamically very unfavourable.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, June 27th*, 1953.]

---

691. *Hydrazine. Part VI.* Salts of Dimethyl Ketazine and Certain Hydrazones. The Halogeno-antimonites and -bismuthites.*

By W. PUGH.

(*With Notes on the Optical Properties of the Crystals.* By H. C. G. VINCENT.)

Chloro-, bromo-, and iodo-antimonites and -bismuthites of dimethyl ketazine, butanone hydrazone, pentan-3-one hydrazone, and heptan-4-one hydrazone have been prepared by crystallisation of mixtures of the halides of antimony and bismuth and hydrazine from ketone–water mixtures, sometimes in strongly acid solutions. The optical properties of the crystals have been examined and preliminary evidence is presented to show that solutions of these salts in acetone are good conductors of electricity.

PART I* of this series described certain chlorostannates, isolated from ketone–water mixtures, which were reported as hydrazinium salts containing ketone of crystallisation. It then seemed unlikely that hydrazine salts and ketones might condense together under the strongly acid conditions prevailing, because the formation of ketazines and hydrazones is held to take place most generally in neutral or alkaline solution. [The work of Gilbert

* Parts I—V, *J.*, 1952, 4138; 1953, 354, 1934, 2491, 2493.

(*J. Amer. Chem. Soc.*, 1929, **51**, 3394), discussed below, shows that dimethyl ketazine is completely hydrolysed in strongly acid solution.] Moreover, ketones had been estimated in these compounds by the 2 : 4-dinitrophenylhydrazone method, which we have now abandoned because its results are about 25% low. In Part II * the authors re-formulated these compounds, tentatively, as salts of dimethyl ketazine and of certain hydrazones, basing their views partly on the remarkable tenacity with which ketone is retained in them when they are heated *in vacuo* to near the melting point, and partly on a revised estimation of ketone by Messinger's method (Goodwin, *J. Amer. Chem. Soc.*, 1920, **42**, 39), the revised value being confirmed by combustion analysis for carbon and hydrogen. Thus, $(N_2H_5)_2SnCl_6,3C_3H_6O$ became $[Me_2C{:}N{\cdot}NH{:}CMe_2]_2SnCl_6$. Salts of these bases had never before been described, but a similar series of bromostannates and bromostannites has since been reported (Part IV *), and the present paper adduces further evidence to characterise them as salts and describes a number of similar salts containing complex anions of antimony and bismuth.

The view that these new compounds are salts is based on the following properties: they are highly crystalline, hard, dense, and salt-like; in colour, and in behaviour towards water, acids, and alkalis, they resemble the corresponding ammonium and potassium salts, the chloro-compounds being colourless, the bromo-compounds yellow, and the iodo-compounds scarlet; they are hydrolysed in water, insoluble basic salts of the heavy metals being precipitated, but, with the exception of the iodo-salts, they dissolve readily in dilute acids, the solutions containing hydrazine salts and free ketone [it is true that they have low melting points (<200°), and decompose when heated above their melting points, but these properties are shared also by the simple hydrazine salts]; they are insoluble in light petroleum, benzene, carbon tetrachloride, chloroform, alcohol, and ether, but are very soluble in ketones. These properties, which are common to the whole class, will not be repeated under the individual salts described later in the Experimental section.

However, the most convincing evidence of their salt character is the fact that acetone solutions of these substances are excellent conductors of electricity. Accurate measurements of conductivities are now in progress and the following approximate values of the molecular conductivity, μ, at dilutions v litres per mole, of (i) dimethyl ketazinium tetrachlorobismuthite, (ii) dimethyl ketazinium tetrachloroantimonite, (iii) bis(dimethyl ketazinium) hexabromostannate, and (iv) tris(dimethyl ketazinium) octadecaiodopenta-antimonite are given to show the order of the conductivities. The measurements were made in acetone solution (undried) at 17°. A value for potassium iodide as a reference electrolyte was obtained at the same time. It being borne in mind that these large ions may have low mobilities, the conductivities indicate that the salts are ionised in acetone solution to approximately the same degree as potassium iodide, and they also indicate the probability that salts (i) and (ii) are binary electrolytes, while salts (iii) and (iv) are, respectively, ternary and quaternary electrolytes.

v (l.)	20	40	100	500	2500
μ, KI	86	—	—	—	—
μ, $C_6H_{13}N_2BiCl_4$, (i)	28	34	43	67	86
μ, $C_6H_{13}N_2SbCl_4$, (ii)	54	—	—	—	—
μ, $(C_6H_{13}N_2)_2SnBr_6$, (iii)	—	70	—	—	—
μ, $(C_6H_{13}N_2)_3Sb_5I_{18}$, (iv)	143	—	—	—	—

The stability of dimethyl ketazine in water has been investigated by Gilbert (*loc. cit.*) who states that it is soluble in water, yielding an alkaline solution, and that if the hydroxyl ions are removed by acids more are produced. In strong mineral acids, it is completely hydrolysed to hydrazinium ions and acetone. Hydrolysis is, however, reversible, involving acetone hydrazonium ion as well as hydrazinium ion, and the measurements show that, even at low acidities, hydrolysis of dimethyl ketazine is extensive, being 30—70% at pH 5 and 40—90% at pH 4·6, the actual proportion depending on the concentration of ketazine. While hydrolysis is promoted by acids, it is repressed by addition of acetone, but, according to a footnote (*loc. cit.*, p. 3402), Gilbert reaches the conclusion that, in presence of acetone, dimethyl ketazine does not function as a base. The

hydrolysis and formation of dimethyl ketazine, according to Gilbert, involve reaction between acetone, hydrazinium ions, and hydrogen ions:

$$Me_2C{:}N{\cdot}N{:}CMe_2 + H^+ + H_2O \rightleftharpoons [Me_2C{:}N{\cdot}NH_3]^+ + Me_2CO$$

and

$$[Me_2C{:}N{\cdot}NH_3]^+ + H_2O \rightleftharpoons [N_2H_5]^+ + Me_2CO$$

On the other hand, Conant and Bartlett (*J. Amer. Chem. Soc.*, 1932, **54**, 2881) suggest that the formation of semicarbazones and related substances proceeds by reaction between neutral molecules of semicarbazide and ketones. This reaction was shown to be catalysed, not only by hydrogen ions, but also by acid molecules in the Brönsted sense. They showed, too, that these semicarbazones, like the ketazines, are progressively hydrolysed at increasing acidities.

Since all these observations were made in very dilute solutions, the conclusions to be drawn from them are not necessarily valid for the concentrated solutions used for the preparation of the ketazinium and hydrazonium salts described in this series. It is particularly to be noted that some of these salts separate from strongly acid solutions—*e.g.*, it needs a very high concentration of hydrobromic acid to keep antimony bromide in solution, even in the presence of hydrazine bromide—while some others are best prepared from strongly acid solution by treatment with less ketone than is theoretically needed—*e.g.*, the bromo- and the iodo-salts. These two facts show that dimethyl ketazinium ions and ketone hydrazonium ions must exist in considerable concentration in strongly acid solution, without the need of excess of ketone to repress hydrolysis; they also make it difficult to sustain Conant and Bartlett's view that condensation occurs between neutral molecules and ketone molecules; neutral molecules of hydrazine are not to be expected in such acid solutions.

It may then be that condensation, under these conditions, proceeds between hydrazinium ions and ketone molecules, as suggested by Gilbert, the process being subject to general acid catalysis, as suggested by Conant and Bartlett. It may be significant in this connection that attempts to make complex fluoro-salts of ketazines and hydrazones have failed (Part III, *loc. cit.*), possibly because the fluoro-acids are relatively inactive catalytically. This cannot, however, be the whole explanation, because attempts to make the chloro- and bromo-aluminates of these bases have also failed (Part V, *loc. cit.*). An important factor, no doubt, is favourable ionic sizes for building up of the crystal pattern.

The complex antimony and bismuth salts, described below, were made from cold or warm aqueous-acid solutions of the component metal salts and hydrazine salts, by treatment with acetone, ethyl methyl ketone, diethyl ketone, or di-*n*-propyl ketone. With one exception, acetone alone yielded ketazinium salts, its homologues yielding hydrazonium salts under similar conditions. The exception is di-*n*-propyl ketone, which yielded its ketazinium heptaiododiantimonite. Crystallisation of this salt proved difficult and the mixture was kept on a boiling-water bath for a few hours to remove excess of ketone. The higher temperature probably accounted for further condensation. The bromo- and iodo-salts produced from the higher ketones crystallised easily, provided the quantity of ketone added was less than was theoretically needed to condense with the hydrazine present; but the slightest excess of ketone caused dissolution of the precipitated salt with separation of a viscous liquid which could not be induced to crystallise; it dried to a gummy mass. The iodo-salts are least soluble and separate most easily. It has not been possible to crystallise any hydrazonium chloro-salts of antimony, or bismuth, for treatment in these cases with ethyl methyl, or diethyl, ketone resulted in the immediate separation of a second phase and neither phase could be induced to crystallise.

Experimental

Analytical Methods.—Hydrazine and antimony were determined by iodate titration (Andrews's method), the latter after having been separated as sulphide; bismuth was determined as oxide, after repeated evaporation with nitric acid and ignition below the m. p.; halogens were determined by Volhard's method. The iodo-compounds required special treat-

ment because they are incompletely decomposed in hot acid solution, even with silver nitrate. Iodo-antimonites were dissolved in sodium hydroxide solution (halogen-free) saturated with hydrogen sulphide, and antimony sulphide was precipitated by acidification with sulphuric acid, a double precipitation being necessary to separate traces of adsorbed iodide; iodide was then determined in the combined filtrates. All ordinary methods of dissolution failed for the iodo-bismuthites and these were dissolved in a small volume of acetone, to which was then added, rapidly, a warm dilute solution of sodium hydroxide. After being boiled, the mixture was filtered and the bismuth hydroxide was dissolved in warm dilute nitric acid; the resulting solution usually carried a trace of adsorbed iodide and was treated separately from the filtrate by Volhard's method.

Carbon and hydrogen determinations were made in the conventional combustion train, but the results, while being of the correct order, are not as good as those for the inorganic constituents. Silbert and Kirner's modification of the combustion tube filling (*Ind. Eng. Chem. Anal.*, 1936, **8**, 353), designed to overcome interference caused by the presence of arsenic, antimony, and other elements, was tried in two instances, but the results were no better. Wherever possible, therefore, direct determinations of acetone and ethyl methyl ketone have been made, by Messinger's method, after distilling off the ketone from dilute acid solution (from dilute alkali, followed by an acid wash to fix hydrazine, in the iodo-antimonites).

Dimethyl Ketazinium Tetrachloroantimonite.—Antimony trichloride (4·56 g.; 1 mol.) and hydrazine monohydrochloride (1·37 g.) or dihydrochloride (2·1 g.; 1 mol.) were dissolved in 3N-hydrochloric acid (5 c.c.), and acetone (5 c.c.) was added. The mixture became hot, and on cooling yielded a mass of needles. Sufficient acetone was then added to redissolve the crystals and the solution was allowed to evaporate slowly in a partly covered vessel, yielding colourless needles of *dimethyl ketazinium tetrachloroantimonite*, m. p. 109—110° (Found: C, 19·1; H, 3·6; N_2H_4, 8·4; Cl, 37·6; Sb, 32·4; C_3H_6O, 30·3. $C_6H_{13}N_2SbCl_4$ requires C, 19·1; H, 3·5; N_2H_4, 8·5; Cl, 37·7; Sb, 32·3; C_3H_6O, 30·1%). A similar, but less pure, product was obtained by boiling a solution of antimony trichloride, in chloroform–acetone (2 : 1), with a suspension of hydrazine monohydrochloride, and washing the solid product with a similar chloroform–acetone mixture.

The crystals, probably monoclinic, are colourless, acicular, (010) plates elongated parallel to crystallographic axis *c*. The optic axial plane is perpendicular to (010). $Bx^a(\widehat{\gamma})c$, 3° (approx.). Bx° is perpendicular to (010). Elongation positive. Optically positive. $2V\gamma(D) = 70°$. Axial dispersion strong, red > violet, and horizontal dispersion apparent. n_D: $\alpha = 1·642$, $\beta = 1·670$, $\gamma = 1·750$. Birefringence very high, $(\gamma - \alpha) = 0·118$.

Dimethyl Ketazinium Tetrabromoantimonite.—Clear solutions containing antimony bromide and hydrazine bromide can be obtained only with a large excess of hydrobromic acid. Antimony trioxide (3 g.) was boiled with concentrated hydrobromic acid (10 c.c.), and the turbid mixture was treated with hydrazine hydrate (50%; 2 g.) and acetone (40 c.c.). The opalescent yellow solution, on slow evaporation in air, deposited a flocculent precipitate, which was filtered off, and the resulting clear yellow solution yielded yellow needles of *dimethyl ketazinium tetrabromoantimonite*, m. p. 112—114° (Found: C, 12·5; H, 2·2; N_2H_4, 5·7; Br, 57·9; Sb, 22·2. $C_6H_{13}N_2SbBr_4$ requires C, 13·0; H, 2·4; N_2H_4, 5·8; Br, 57·8; Sb, 22·0%). A peculiarity, unique to this salt, is that it seems to undergo slow decomposition; the antimony and bromide content remain practically unchanged, but the hydrazine titre diminishes, and more and more ammonia is found in the product.

The crystals are monoclinic, well-formed, yellow pinacoids, modified by prism and dome faces, elongated parallel to *c*; or they are slender needles with the same elongation. They are colourless in mounts and show a good (010) cleavage. The optic axial plane is perpendicular to (010). $Bx^a(\gamma)$ is inclined 10° to *c* in the symmetry plane. Optically positive. $2V(D) = 49\frac{1}{2}°$. Axial dispersion moderate, red > violet; horizontal dispersion apparent. n_D: $\alpha = 1·741$, $\beta = 1·761$, $\gamma = 1·86$ (calc.). Birefringence high, $(\gamma - \alpha) = 0·12$.

Butanone Hydrazonium Tetrabromoantimonite.—Antimony trioxide (2 g.) and hydrazine hydrate (50%; 2 g.) were warmed together with concentrated hydrobromic acid, a large excess of acid being necessary to get complete solution. The warm solution was then treated, drop by drop with good mixing, with ethyl methyl ketone (0·8 c.c.), a yellow precipitate being formed at once. This redissolved on warming to yield a clear yellow solution, which gave yellow crystals of *butanone hydrazonium tetrabromoantimonite* (4 g.), m. p. 123—125° (Found: C, 8·6; H, 2·4; N_2H_4, 6·1; Br, 60·4; Sb, 23·0; C_4H_8O, 13·8. $C_4H_{11}N_2SbBr_4$ requires C, 9·1; H, 2·1; N_2H_4, 6·1; Br, 60·5; Sb, 23·0; C_4H_8O, 13·6%). The quantity of ketone added (0·8 c.c.) was

approx. 80% of that required to condense all the hydrazine present. An excess of ketone caused separation of a yellowish, heavy, oily layer which contained the whole of the hydrazonium salt and did not crystallise.

The crystals are monoclinic, with modified pinacoidal habit, somewhat elongated parallel to *c*. Cleavage absent, and colourless in mounts. The optic axial plane is parallel to (010), and $Bx^a(\alpha)$ is inclined at about 40° to *c*. Negative. $2V(\alpha) = 75°$ (approx.). Axial dispersion perceptible, red > violet. n_D : $\beta = 1{\cdot}84$ (approx.). Birefringence moderate.

Pentan-3-one Hydrazonium Tetrabromoantimonite.—This *salt* was made in the same way as the butanone hydrazonium salt described above, with similar quantities of reagents and diethyl ketone. It forms pale yellow crystals, m. p. 90—92°, which yield a yellow melt (Found: C, 10·8; H, 2·4; N_2H_4, 5·9; Br, 58·9; Sb, 22·4. $C_5H_{13}N_2SbBr_4$ requires C, 11·0; H, 2·4; N_2H_4, 5·9; Br, 58·9; Sb, 22·5%).

The crystals are monoclinic pinacoids, often with oblique termination and flattened parallel to (010), and elongated parallel to *c*. Cleavage is absent, and the colour in mounts is very pale yellow. The optic axial plane is parallel to (010) and $Bx^a(\alpha)$ is inclined at about 43° to *c*. Optically negative. $2V(\alpha) = 50—55°$. Axial dispersion marked, red < violet. n_D: $\alpha = 1{\cdot}79$, $\beta = 1{\cdot}83$ (approx.), γ (not determined). Birefringence moderate.

Tris(dimethyl Ketazinium) Octadecaiodopenta-antimonite.—Antimony trioxide (1·5 g., 1 mol.) was dissolved in the minimum quantity of hydriodic acid (*d* 1·5; 10 c.c.), and the solution, after having been filtered from a small black residue, was diluted with an equal volume of water and treated with hydrazine hydrate (50%; 2 g., 2 mols.) previously neutralised with hydriodic acid. The clear, dark orange solution was then treated with acetone; a yellow powder was precipitated; good crystals were obtained by adding warm acetone, cooling, and recrystallising from acetone–water (2 : 1). The ruby-red crystals of *tris(dimethyl ketazinium) octadecaiodopenta-antimonite*, dried *in vacuo*, had m. p. 153—154° [Found: C, 7·1; H, 1·3; N_2H_4, 3·0; I, 70·5; Sb, 18·8; C_3H_6O, 11·0. $(C_6H_{13}N_2)_3Sb_5I_{18}$ requires C, 6·7; H, 1·2; N_2H_4, 3·0; I, 70·6; Sb, 18·8; C_3H_6O, 10·8%]. The composition of this salt is so unusual that particular efforts were made to establish its identity. Several preparations were made, varying the proportions of antimony to hydrazine from 0·5 to 2·0, and the conditions of crystallisation; in some cases, too, fractional crystallisation was used. In every case, the product had the above composition. (All the iodoantimonites described herein are decomposed with difficulty by acids; the best solvent for their analysis is sodium hydroxide containing hydrogen sulphide. They are also sparingly soluble in chloroform, alcohol, and ether, but insoluble in benzene, light petroleum, and carbon tetrachloride.)

The crystals are biaxial, poorly shaped grains with no pronounced cleavage but some tendency to elongation, reddish orange in mounts. Optically negative. $2V(\alpha)$ very large. Axial dispersion distinct, red < violet. Elongation negative. Pleochroism distinct, with maximum absorption (deep orange yellow) for vibrations perpendicular to the elongation, and pale orange yellow for vibrations parallel to the elongation. n_D of α is much above 1·84. Birefringence, very high. System uncertain.

Butanone Hydrazonium Tetraiodoantimonite.—A warm, clear orange solution of antimony oxide and hydrazine iodide in hydriodic acid, prepared as described for the above ketazinium salt, was treated, drop by drop, with ethyl methyl ketone (1 c.c.), yielding an orange precipitate. (An excess of ketone caused separation of a dark red oil which could not be crystallised.) The mixture was cooled well, and the crystals of *butanone hydrazonium tetraiodoantimonite* were recrystallised from hot dilute hydriodic acid (in which they are sparingly soluble), yielding dark orange prisms, m. p. 153—154° (Found: N_2H_4, 4·4; I, 71·1; Sb, 17·2; C_4H_8O, 9·9. $C_4H_{11}N_2SbI_4$ requires N_2H_4, 4·4; I, 71·0; Sb, 17·0; C_4H_8O, 10·0%).

The crystals are monoclinic, showing stout pinacoidal forms with minor prism faces and well developed dome and pyramid termination; elongated parallel to *c*. They show poor cleavage, and simple twinning is common. Brownish-yellow in mounts. The optic axial plane is parallel to (010). One bisectrix makes an angle of 40° with *c* in the symmetry plane. Optically negative. $2V(\alpha) = 80°$ (estimated). Axial dispersion moderate, red > violet. Slightly pleochroic in yellow and brownish-yellow. n_D of α much above 1·84 and birefringence high.

Pentan-3-one Hydrazonium Tetraiodoantimonite.—This *salt* was prepared as described above for the butanone hydrazonium salt, but with diethyl ketone. However, it is increasingly difficult to get pure products from the higher ketones, the precipitates being contaminated with antimony iodide. The best product was obtained by fractional precipitation, discarding the first fractions, and allowing the mixture to cool slowly while small quantities of ketone were added. The product, after recrystallisation from hot dilute hydriodic acid and a trace of

hydrazine iodide, was a coarsely crystalline, dark orange powder, m. p. 150—151° (Found: N_2H_4, 4·4; I, 69·6; Sb, 16·9. $C_5H_{13}N_2SbI_4$ requires N_2H_4, 4·4; I, 69·5; Sb, 16·7%).

The crystals are monoclinic with a pinacoidal habit and elongation parallel to *c*. Simple twinning is common. They are brownish-yellow in mounts. The optic axial plane is parallel to (010) and a bisectrix makes an angle of 35—40° with *c* in the symmetry plane. Optically negative. $2V(\alpha) = 80°$ (estimated). Axial dispersion perceptible, with red < violet. Slightly pleochroic in yellow and brownish yellow. n_D of α much above 1·84 and birefringence high.

Di-n-propyl Ketazinium Heptaiododiantimonite.—A warm, clear, orange solution containing antimony and hydrazine iodides in mol. ratio 1 : 1, and made as described for the above iodoantimonites, was treated with small amounts of di-*n*-propyl ketone. A heavy, red layer separated immediately. The mixture was shaken vigorously for several minutes, the aqueous layer was poured off, and the thick plastic, gummy residue was washed with dilute hydriodic acid. As the *salt* did not crystallise in the course of several days, even *in vacuo*, it was dried at 100° to constant weight (Found: C, 12·9; H, 2·4; N_2H_4, 2·4; I, 65·8; Sb, 17·9. $C_{14}H_{29}N_2Sb_2I_7$ requires C, 12·4; H, 2·1; N_2H_4, 2·4; I, 65·5; Sb, 17·9%). Examination under the polarising microscope showed it to be a crystalline material gummed together by uncrystallised liquor. The crystals appeared to be a single compound but they were too small for optical study.

Dimethyl Ketazinium Tetrachlorobismuthite.—Bismuth oxychloride (10 g., 1 mol.) and hydrazine dihydrochloride (4 g., 1 mol.) were dissolved in 5N-hydrochloric acid (10 c.c.), and the solution was poured into acetone (15 c.c.). The mixture became warm and slowly deposited colourless needles of *dimethyl ketazinium tetrachlorobismuthite* which, after recrystallisation from acetone, had m. p. 139—141° (Found: C, 15·0; H, 2·8; N_2H_4, 6·9; Cl, 30·6; Bi, 45·1; C_3H_6O, 24·8. $C_6H_{18}N_2BiCl_4$ requires C, 15·5; H, 2·8; N_2H_4, 6·9; Cl, 30·6; Bi, 45·0; C_3H_6O, 25·0%). Its composition, and that of the bromo-salt described immediately below, was unchanged after 12 months.

The crystals are monoclinic, with an elongated prismatic and bladed habit, colourless in mounts, and without any pronounced cleavage. The optic axial plane is perpendicular to (010) and $Bx^a(\gamma)$ is inclined about 15° to *c* in the symmetry plane. Optically positive, $2V(D) = 53°$. Axial dispersion is marked, with red > violet, and horizontal dispersion is distinct. Length positive. n_D: $\alpha = 1{\cdot}668$, $\beta = 1{\cdot}688$, $\gamma = 1{\cdot}80$. Double refraction very high, $(\gamma - \alpha) = 0{\cdot}13$.

Dimethyl Ketazinium Tetrabromobismuthite.—Concentrated solutions of bismuth tribromide and hydrazine hydrobromide, made respectively from bismuth carbonate and hydrazine hydrate and hydrobromic acid, were mixed in approximately equimolar proportions and treated with three volumes of acetone. The mixture became warm and clear and on slow evaporation in a partly covered vessel gave yellow needles, which, after recrystallisation from aqueous acetone, proved to be pure *dimethyl ketazinium tetrabromobismuthite*, m. p. 144—146° (Found: C, 11·1; H, 2·0; N_2H_4, 4·9; Br, 50·0; Bi, 32·5; C_3H_6O, 17·6. $C_6H_{18}N_2BiBr_4$ requires C, 11·2; H, 2·0; N_2H_4, 5·0; Br, 49·9; Bi, 32·6; C_3H_6O, 18·1%).

The crystals are probably monoclinic and show somewhat elongated simple pinacoidal forms with dome terminations. They are colourless in mounts and have no pronounced cleavage. Optically positive, $2V(D) = 31°$. Dispersion very strong, red < violet, giving rise to imperfect extinction and anomalous interference colours in parallel light, in sections perpendicular to the bisectrices. Elongation is positive. n_D of $\beta = 1{\cdot}8$ (approx.), the crystals being somewhat attacked by immersion liquids. Double refraction rather high.

Butanone Hydrazonium Tetrabromobismuthite.—A hot solution, obtained by warming bismuth trioxide (2·3 g., 1 mol.) with concentrated hydrobromic acid (4 c.c.) and hydrazine hydrobromide (1·13 g., 1 mol.), was treated, drop by drop and with vigorous stirring, with ethyl methyl ketone (0·8 c.c.). The liquid was cooled, an emulsion separating which crystallised on vigorous shaking. Subsequent cooling to 0° for a few hours yielded a crop (3 g.) of yellow prisms, *butanone hydrazonium tetrabromobismuthite*, m. p. 149—152° (Found: N_2H_4, 5·3; Br, 52·2; Bi, 34·0. $C_4H_{11}N_2BiBr_4$ requires N_2H_4, 5·2; Br, 52·0; Bi, 34·0%). The salt yields an orange-coloured melt which decomposes above the m. p.

The crystals are monoclinic, minute grains, and occasionally pinacoidal laths elongated parallel to *c*; colourless in mounts and with no cleavage. The optic axial plane is perpendicular to (010). Negative. $2V = 50°$ (approx.). Axial dispersion perceptible, red > violet. $Bx^a(\alpha)$ makes an angle of 35—40° with *c*. Attacked by available liquids, and refractive indices not determined. Birefringence moderate.

Pentan-3-one Hydrazonium Tetrabromobismuthite.—This *salt* was made in the same way as the above butanone derivative, but with diethyl ketone. The crystals are yellow prisms,

m. p. 120—124° (decomp.) (Found: C, 9·0; H, 2·1; N_2H_4, 5·1; Br, 51·0; Bi, 33·0. $C_5H_{13}N_2BiBr_4$ requires C, 9·5; H, 2·1; N_2H_4, 5·1; Br, 51·0; Bi, 33·2%). For the preparation of this and the salt previously described the quantity of ketone added must be less than is required to condense with all the hydrazine present, otherwise uncrystallisable viscous solutions are formed.

The crystals are monoclinic, with pinacoidal habit and elongated parallel to *c*. Cleavage is absent, and the colour in mounts is very pale yellow. The optic axial plane is parallel to (010) and $Bx^a(\alpha)$ is inclined at about 25° to *c*. Optically negative. $2V(\alpha) = 50$—55°. Axial dispersion marked, red > violet. n_D of $\beta > 1{\cdot}84$. Birefringence moderate.

Dimethyl Ketazinium Tetraiodobismuthite.—Bismuth iodide (5·9 g., 1 mol.) and hydrazinium iodide, prepared by adding a slight excess of hydriodic acid to hydrazine hydrate (50%; 1 g., 1 mol.), were warmed with acetone (20 c.c.), and the blood-red solution was filtered and evaporated slowly. The crude product was recrystallised from warm acetone–water (4 : 1), yielding ruby-red crystals of *dimethyl ketazinium tetraiodobismuthite*, m. p. 110° (decomp.). They were dried on paper and *in vacuo* (Found: N_2H_4, 3·9; I, 61·0; Bi, 25·4; C_3H_6O, 14·3. $C_6H_{13}N_2BiI_4$ requires C, 3·9; I, 61·3; Bi, 25·2; C_3H_6O, 14·0%). This salt, and all the other iodobismuthites described, are sparingly soluble in chloroform, alcohol, and ether, but insoluble in light petroleum, benzene, and carbon tetrachloride.

Monoclinic or triclinic, very minute, anhedrons, with no cleavage, and a deep red colour by transmitted light, even for the smallest grains, precluding precise optical determinations. Negative. $2V = 50°$ (approx.). Dispersion not perceptible. Strongly pleochroic in deep red and orange-red. n_D of α much above 1·84.

Butanone Hydrazonium Tetraiodobismuthite.—Half of the quantities of bismuth iodide and hydrazinium iodide used in the above preparation were digested on the water-bath with water (20 c.c.) until no more bismuth iodide would dissolve. The residue was filtered off and the filtrate was kept warm while ethyl methyl ketone (0·5 g.) was added. Slow addition of ketone, one drop per min., gave a well crystallised orange powder, *butanone hydrazonium tetraiodobismuthite*, which, after being dried *in vacuo*, had m. p. 162—164° (Found: N_2H_4, 4·0; I, 63·3; Bi, 26·0. $C_4H_{11}N_2BiI_4$ requires N_2H_4, 4·0; I, 63·3; Bi, 26·0%). Excess of ketone dissolves the salt, yielding a dark red liquid which is difficult to crystallise.

Crystals are monoclinic, minute, doubly-terminated prisms and pinacoids, somewhat elongated and with no cleavage, deep red in colour in mounts. The optic axial plane is probably parallel to (010), a bisectrix making an angle of 40—45° with the elongation, in the symmetry plane. Negative. $2V$ is large (70—80°) and dispersion is perceptible. Moderately pleochroic in dark red and light red. n_D for α, β, and γ much above 1·84. Birefringence rather high.

Pentan-3-one Hydrazonium Tetraiodobismuthite.—This *salt* was made in the same way as the butanone hydrazonium salt described above, but with diethyl ketone; it separates as ruby-red crystals, m. p. 169—170° (Found: C, 7·1; H, 1·6; N_2H_4, 4·0; I, 62·2; Bi, 25·8. $C_5H_{13}N_2BiI_4$ requires C, 7·3; H, 1·6; N_2H_4, 3·9; I, 62·3; Bi, 25·6%). This salt also dissolves in the slightest excess of ketone, giving uncrystallisable viscous liquids.

The crystals are monoclinic with well-marked pinacoidal habit, and (010) strongly developed, modified by dome and prism faces and elongated parallel to *c*. Cleavage is absent. The colour in mounts is deep red. The optic axial plane is parallel to 010), and Bx^a makes an angle of 40—45° with *c*. Negative. $2V$ (α) 70—80°. Dispersion perceptible. Red < violet. Rather strongly pleochroic in dark red and lighter red.

n_D for α, β, γ, much over 1·84. Birefringence rather high.

The authors thank Mr. R. von Holdt, B.Sc., and Mr. M. C. B. Hotz, B.Sc., for carrying out the combustion analyses and some of the ketone estimations respectively, and Mr. I. R. Morrison for making the conductivity measurements.

Departments of Chemistry and Geology,
University of Capetown.

[*Received, July 6th,* 1953.]

692. *The Scope and Mechanism of Carbohydrate Osotriazole Formation. Part I. The Action of Copper Sulphate on Glucose Methylphenylosazone and Glucose 2-N′-Methyl-1-N′ : 2-N′-diphenylosazone.*

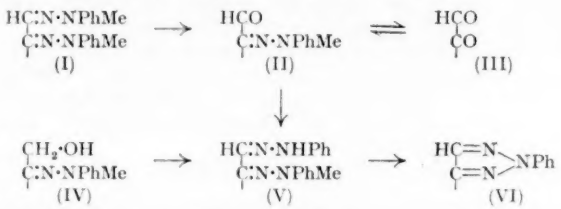
By H. El Khadem.

Under the action of copper sulphate glucose 2-*N*′-methyl-1-*N*′ : 2-*N*′-diphenylosazone (V) gives an osotriazole, but glucose *N*-methyl-*N*-phenylosazone (I) loses its hydrazone residues stepwise, finally yielding glucosone. This difference is attributed to the presence in the former of hydrogen attached to nitrogen.

Carbohydrate phenylosazones are converted into phenylosotriazoles (VI) and aniline when refluxed in suspension in aqueous copper sulphate (Hann and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 735). Osazones derived from other aromatic monosubstituted hydrazines behave similarly (Hardegger and El Khadem, *Helv. Chim. Acta*, 1947, **30**, 1949; 1950, **33**, 253).

For a similar reaction osazones derived from disubstituted hydrazines would require to lose one of the groups attached to nitrogen, and this seems unlikely. In accordance with this, the reaction of glucose methylphenylosazone (I) with aqueous copper sulphate, although vigorous, was found to yield glucosone 2-methylphenylhydrazone (II), one hydrazone residue being eliminated by hydrolysis. On further treatment of (II), or on prolonged treatment of (I), with copper sulphate the second hydrazone residue was also eliminated and glucosone (III) was obtained in nearly 80% yield. This behaviour is similar to that of carbohydrate hydrazones, which with copper sulphate yield the parent sugar nearly quantitatively; the hydrazones are first hydrolysed and the hydrazines produced are then oxidised with copper sulphate (El Khadem, Diss., Zurich, 1950).

The structure of (II) was established by comparison with glucosone methylphenylhydrazone prepared, according to Fischer (*Ber.*, 1889, **22**, 90), by treating glucosone (III) with *N*-methyl-*N*-phenylhydrazine; the crystalline tetra-acetates and tetrabenzoates were also identical. Fischer did not establish whether the methylphenylhydrazone residue was attached to $C_{(1)}$ or $C_{(2)}$. To settle this, the hydrazone (II) was treated with phenylhydrazine; the resultant mixed osazone (V) was identical with glucose 2-*N*′-methyl-1-*N*′ : 2-*N*′-diphenylosazone, (V), prepared according to Percival (*J.*, 1941, 750) by treating fructose methylphenylhydrazone (IV) with phenylhydrazine.



Glucose 2-*N*′-methyl-1-*N*′- : 2-*N*′-diphenylosazone (V) with copper sulphate yielded glucose phenylosotriazole and methylaniline; this osazone has a hydrogen atom attached to a nitrogen atom, resembling in this respect the simple osazones. Osotriazole formation probably takes place by the elimination of this hydrogen atom together with the NPhMe group from the neighbouring methylphenylhydrazone residue, forming methylaniline.

These experiments indicate that for the conversion of an osazone into an osotriazole at least one hydrazone residue must carry a hydrogen atom attached to the nitrogen atom. If this hydrogen atom is replaced by an alkyl group stepwise hydrolysis of the hydrazine residue occurs, yielding, as final product, the osone in good yield. The latter reaction can advantageously be used as a starting point for the synthesis of ascorbic acid analogues.

Further experiments are in progress.

Experimental

Glucosone 2-Methylphenylhydrazone.—Glucose methylphenylosazone (7 g.) in dioxan (100 ml.) was added in portions to a boiling solution of copper sulphate (5 g.) in water (100 ml.); after the initial vigorous reaction had subsided the mixture was refluxed for 10 min. and filtered hot from the precipitated copper. The excess of copper sulphate was removed by passing in hydrogen sulphide, filtering, adding barium carbonate, and filtering again. The clear filtrate was evaporated to dryness; on addition of a few drops of methanol the residue crystallised and was purified by recrystallisation from hot water. The pure product, which was faintly yellow, melted at 168°, alone or mixed with glucosone methylphenylhydrazone prepared by Fischer's method (*loc. cit.*) (Found: C, 55·2; H, 6·6; N, 10·1. Calc. for $C_{13}H_{18}O_5N_2$: C, 55·3; H, 6·4; N, 9·9%); it had $[\alpha]_D$ −266° (*c*, 1·15 in pyridine).

The *tetra-acetate*, m. p. and mixed m. p. 118° (from methanol), $[\alpha]_D$ +83° (*c*, 1 in MeOH) (Found: C, 55·8; H, 5·9; N, 6·5. $C_{21}H_{26}O_9N_2$ requires C, 56·0; H, 5·8; N, 6·2%), and *tetrabenzoate*, m. p. and mixed m. p. 187° (from methanol), $[\alpha]_D$ +38° (*c*, 1·09 in $CHCl_3$) (Found: C, 70·6; H, 5·1; N, 4·3. $C_{41}H_{34}O_9N_2$ requires C, 70·5; H, 4·9; N, 4·1%), were prepared from both samples of the hydrazone by treatment with acetic anhydride or benzoyl chloride respectively in pyridine for 24 hr. at room temperature.

Glucosone.—(a) *From glucosone 2-methylphenylhydrazone.* The hydrazone (0·5 g.) was suspended in water (10 ml.) and added in portions to a boiling solution of copper sulphate (0·5 g.) in water (12 ml.), and the mixture was refluxed for 1 hr. and filtered hot. The filtrate was freed from excess of copper sulphate as above, decolourised with charcoal, and evaporated to dryness, giving a colourless glassy mass of glucosone. To eliminate all traces of inorganic matter, the crude osone was redissolved in water (20 ml.) and passed through a cation-exchange and then through an anion-exchange resin. On evaporation of the solution, glucosone was obtained (0·5 g., 79%), having $[\alpha]_D$ −3° (*c*, 1 in H_2O).

(b) *From glucose methylphenylosazone.* The osazone (2 g.) was suspended in a solution of copper sulphate (1 g.) in water (25 ml.). The mixtue was refluxed for 1 hr., filtered hot, and then treated as in (a). The product (0·7 g., 75%) had $[\alpha]_D$ −3° (*c*, 1·1 in H_2O).

A 10% solution of this glucosone in water (15 ml.) reacted in the cold with phenyl hydrazine (2 g.) and acetic acid (0·5 ml.) to give glucose phenylosazone (2·9 g., 97%).

When the glucosone was applied to Whatmann No. 1 filter paper, chromatographed with collidine, and sprayed with ammoniacal silver nitrate only one spot developed which had $R_F = 0·21$; the R_F value in phenol–water was 0·13. No movement occurred with butanol saturated with water.

Glucose 2-N′-Methyl-1-N′ : 2-N′-diphenylosazone.—Glucose methylphenylhydrazone (1 g.) in water (5 ml.) was treated with phenylhydrazine (0·4 g.) in 10% acetic acid (5 ml.) and left at 30° for 2 hr. The crystalline osazone which separated was twice recrystallised from alcohol–water; it had m. p. 193°, $[\alpha]_D$ −59·7° ⟶ +5° (*c*, 1·09 in pyridine) (Found: C, 61·6; H, 6·7; N, 15·2. Calc. from $C_{19}H_{24}O_4N_4$: C, 61·3; H, 6·6; N, 15·1%).

This osazone, prepared by Percival's method (*loc. cit.*), had m. p. and mixed m. p. 193°, $[\alpha]_D$ −59·5° ⟶ +6° (*c*, 1 in pyridine) (Found: C, 61·1; H, 6·6%).

Glucose Phenylosotriazole.—The foregoing osazone (0·5 g.) was suspended in water (10 ml.) and added in portions to a boiling solution of copper sulphate (0·5 g.) in water (10 ml.), then refluxed for 1 hr. and filtered hot. The filtrate was freed from excess of copper sulphate as before, the solution evaporated to dryness, and the residue (0·25 g.) recrystallised from ethanol. The product had m. p. and mixed m. p. 196°, $[\alpha]_D$ −81·7° (*c*, 1 in pyridine).

The author is indebted to Professors R. P. Linstead, F.R.S., H. N. Rydon, N. Fakhouri, and G. Soliman for their interest and valuable suggestions.

Chemistry Department, Faculty of Science,
Alexandria University, Alexandria.

[*Received, July 10th,* 1953.]

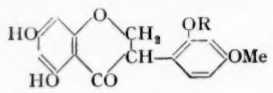
693. *The Synthesis of Homoferreirin.*

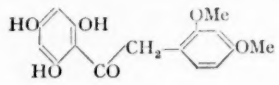
By K. G. Neill.

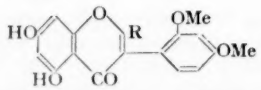
This paper describes the unambiguous synthesis of 5 : 7-dihydroxy-2′ : 4′-dimethoxy*iso*flavanone which is identical with homoferreirin.

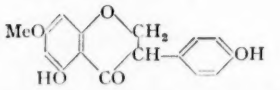
Two phenols, ferreirin and homoferreirin, were isolated from the heartwood of *Ferreirea spectabilis* (King, Grundon, and Neill, *J.*, 1952, 4580) and from degradation studies were assigned the *iso*flavanone structures (I; R = H) and (I; R = Me), respectively (King and Neill, *J.*, 1952, 4752). The synthesis of 5 : 7-dihydroxy-2′ : 4′-dimethoxy*iso*flavanone confirms the structure of homoferreirin.

The 2 : 4-dimethoxyphenylacetonitrile required for the conversion into the deoxybenzoin (II) was prepared in low yield from ethyl 2 : 4-dimethoxyphenylacetate, *via* the amide; but the azlactone method (Mitter and Maitra, *J. Chem. Soc., India*, 1936, **13**, 236) was found to be more convenient. Although the deoxybenzoin failed to condense with ethyl formate in the presence of sodium (cf. *idem, loc. cit.*, Baker, Chadderton, Harborne, and Ollis, *J.*, 1953, 1852), it was readily converted into the *iso*flavone ester (III; R = CO_2Et) in good yield by ethoxalyl chloride (Baker and Ollis, *Nature*, 1952, **169**, 706). On


(I)


(II)


(III)


(IV)

hydrolysis with cold dilute sodium hydroxide, the acid (III; R = CO_2H) was obtained and this when heated above its melting point gave 5 : 7-dihydroxy-2′ : 4′-dimethoxy*iso*flavone (III; R = H). Although this *iso*flavone was not sufficiently soluble for it to be hydrogenated at room temperature and pressure its diacetate was readily hydrogenated with palladium–charcoal catalyst to the *iso*flavanone diacetate. The latter on mild alkaline hydrolysis gave 5 : 7-dihydroxy-2′ : 4′-dimethoxy*iso*flavanone which was identical with natural homoferreirin.

The isolation from the bark of *Prunus puddum* of another *iso*flavanone, padmakastein (dihydroprunetin) (IV) by Narasimhachar and Seshadri (*Proc. Indian Acad. Sci.*, 1952, **35**, *A*, 202) suggests that this hitherto undiscovered class of compound may be more widely spread in Nature than has been realised.

Experimental

Microanalyses are by Mrs. S. M. Bark, B.Sc., of Nottingham.

2 : 4-*Dimethoxyphenylacetonitrile*.—Ethyl 2 : 4-dimethoxyphenylacetate (10·3 g.) (Pschorr and Knoffer, *Annalen*, 1911, **382**, 56) was heated in a sealed tube with ammonia solution (25 ml.; *d* 0·88) for 3 hr. On cooling, the *amide* separated and crystallised from benzene–light petroleum (b. p. 60—80°) as rectangular plates (7·2 g.), m. p. 130—131° (Found: C, 61·8; H, 7·0; N, 7·2. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·7; N, 7·2%). 2 : 4-Dimethoxyphenylacetic acid (2·1 g.) was recovered by acidifying the filtrate. The amide (7·0 g.) was heated under reflux with phosphorus oxychloride (100 ml.) for 1 hr. The residue obtained after removal of excess of phosphorus oxychloride was dissolved in chloroform, the solution washed, the solvent evaporated, and the product chromatographed in benzene on alumina. Concentration of the eluate gave the nitrile (1·9 g.) as needles, m. p. 76° (Found: C, 67·5; H, 6·2; N, 8·0. Calc. for $C_{10}H_{11}O_2N$: C, 67·8; H, 6·3; N, 7·9%) (Mitter and Maitra, *loc. cit.*, give m. p. 76°).

2 : 4-*Dimethoxybenzyl* 2 : 4 : 6-*Trihydroxyphenyl Ketone* (II).—This was prepared from the above nitrile by Mitter and Maitra's method (*loc. cit.*). The ketone (2·76 g.) separated from

aqueous methanol as needles, m. p. 178° (Found: C, 63·1; H, 5·7; OMe, 20·2. Calc. for $C_{16}H_{16}O_6$: C, 63·1; H, 5·3; 2OMe, 20·4%).

5 : 7-*Dihydroxy*-2′ : 4′-*dimethoxy*isoflavone-2-*carboxylic Acid* (III; R = CO_2H).—The deoxybenzoin (0·5 g.) in pyridine (1 ml.) was treated with ethoxalyl chloride (1 ml.), and after 1 hr. the mixture was treated with water and extracted with ether. The ethereal solution was washed with 2N-hydrochloric acid and the *ethyl* 5 : 7-*dihydroxy*-2′ : 4′-*dimethoxy*isoflavone-2-*carboxylate*, obtained on evaporation crystallised from methanol, forming yellow leaflets (0·48 g.), m. p. 204—206° (Found: C, 60·9; H, 5·1; OMe, 23·0; loss at 150°, 2·2. $C_{20}H_{18}O_8,0·5H_2O$ requires C, 60·7; H, 4·8; 3OMe, 23·5; loss, 2·3%). It gave a purple colour with ferric chloride and a red precipitate on acidification after reduction with sodium amalgam. The ester (1·1 g.) in 2N-sodium hydroxide (20 ml.) was kept at room temperature for 24 hr. Acidification precipitated the *acid* which crystallised from methanol in yellow plates (0·9 g.), m. p. 266—268° (decomp.) (Found: C, 57·8; H, 4·0; loss at 150°, 4·8. $C_{18}H_{14}O_8,H_2O$ requires C, 57·5; H, 4·3; loss, 4·8%).

5 : 7-*Dihydroxy*-2′ : 4′-*dimethoxy*isoflavone (III; R = H).—The acid (0·5 g.) and copper bronze (10 mg.) were heated in three portions at 300—330° until effervescence ceased. Extraction of the residues with acetone gave 5 : 7-*dihydroxy*-2′ : 4′-*dimethoxy*isoflavone which crystallised from methanol as cream needles (0·27 g.), m. p. 219—220° (Found: C, 64·9; H, 4·6; OMe, 19·3. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5; 2OMe, 19·7%). The *diacetate*, prepared with acetic anhydride and anhydrous sodium acetate, crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as needles, m. p. 200—201° (Found: C, 63·1; H, 4·3; OAc, 30·1. $C_{21}H_{18}O_8$ requires C, 63·3; H, 4·6; 3OAc, 32·4%. The total volatile acid is calculated as acetyl; this includes the molecule of formic acid liberated by the alkaline hydrolysis of the *iso*flavone). This acetate (0·2 g.) was heated under reflux for 24 hr. in acetone (25 ml.) with anhydrous potassium carbonate (1 g.) and methyl sulphate (0·14 ml.), yielding 5 : 7 : 2′ : 4′-tetramethoxy*iso*flavone (0·15 g.) which separated from methanol in rhombs, m. p. and mixed m. p. with a specimen prepared from homoferreirin 204° (Found: C, 66·2; H, 5·3. Calc. for $C_{19}H_{18}O_6$: C, 66·7; H, 5·3%).

5 : 7-*Dihydroxy*-2′ : 4′-*dimethoxy*isoflavanone (I; R = Me) (*Homoferreirin*).—5 : 7-Diacetoxy-2′ : 4′-dimethoxy*iso*flavone (0·7 g.) in acetic acid was hydrogenated over palladised charcoal; the 5 : 7-*diacetoxy*-2′ : 4′-*dimethoxy*isoflavanone (0·3 g.) crystallised from methanol in needles, m. p. 144° (Found: C, 62·6; H, 4·9; OMe, 15·4. $C_{21}H_{20}O_8$ requires C, 63·0; H, 5·1; 2OMe, 15·5%). The *iso*flavanone (0·3 g.) was shaken intermittently with 2N-sodium hydroxide (30 ml.) for 24 hr. Acidification gave 5 : 7-*dihydroxy*-2′ : 4′-*dimethoxy*isoflavanone which crystallised from aqueous methanol in rectangular plates (0·22 g.), m. p. and mixed m. p. with a natural specimen of homoferreirin 168—169° (Found: C, 64·2; H, 5·0; OMe, 18·9. $C_{17}H_{16}O_6$ requires C, 64·6; H, 5·1; 2OMe, 19·4%). The *iso*flavanone (0·15 g.) was heated under reflux for 24 hr. in acetone (20 ml.) with anhydrous potassium carbonate (2 g.) and methyl sulphate (0·20 ml.) yielding 5 : 7 : 2′ : 4′-tetramethoxy*iso*flavanone (0·13 g.) which crystallised from benzene–light petroleum (b. p. 60—80°) in needles, m. p. and mixed m. p. with dimethylhomoferreirin 163°.

The author thanks Professor F. E. King for his continued interest, and gratefully acknowledges a Research Studentship from British Celanese Limited.

THE UNIVERSITY, NOTTINGHAM. [*Received, July 18th*, 1953.]

694. *The Catalytic Deuteration of Organic Compounds. Part III.* Exchange Reactions of Saturated Aliphatic Carboxylic Acids.*

By J. Bell, T. Hill, K. A. Macdonald, R. I. Reed, and (in part) A. Macdonald.

The replacement of the carbon-bound hydrogen in a number of carboxylic acids during homogeneous reaction in solution in deuterium oxide and during reaction in presence of a platinum catalyst has been re-examined, and a more detailed study made of the distribution of deuterium in propionic acid deuterated by each method. Chemical degradation of the deuterated propionic acids has shown that in the homogeneous reaction deuterium replaced only those hydrogen atoms attached to the α-carbon atom, whereas, in the reaction in presence of the catalyst, simultaneous replacement of all carbon-bound hydrogen appeared to occur. This is supported by preliminary information from a study of the cracking patterns in the mass spectrometer of specimens of methyl propionate derived from the deuterated propionic acids.

Early investigations of the homogeneous reaction involving the exchange of the carbon-bound hydrogen atoms of acetic acid dissolved in deuterium oxide led to conflicting results (Lewis and Schutz, *J. Amer. Chem. Soc.*, 1934, **56**, 493; Hall, Bowden, and Jones, *ibid.*, p. 750; Munzberg, *Z. physikal. Chem.*, 1935, **13**, *B*, 21; Lazareff, *Compt. rend.*, 1935, **200**, 1671; Erlenmeyer, Schoenauer, and Schwarzenbach, *Helv. Chim. Acta*, 1937, **20**, 726; Liotta and La Mer, *J. Amer. Chem. Soc.*, 1937, **59**, 946), but the nature of this reaction has been clarified to some extent by Bok and Gieb (*Z. physikal. Chem.*, 1939, **183**, *A*, 353) who showed that exchange with deuterium takes place readily with the hydrogen atoms of the methyl group, the reaction being promoted by acid–base catalysis. The suggested mechanism, involving enolisation, was analogous to that proposed for the deuteration of acetone, although the experimental results are not inconsistent with alternative mechanisms.

In an examination of the exchange reactions of a series of monocarboxylic acids in dilute deuterium oxide, Ives (*J.*, 1938, 81) reported that, among the saturated aliphatic acids, no detectable exchange occurred at 100° in the cases of propionic, *n*-butyric, and *iso*-butyric acids, but subsequently Schanzer and Clusius (*Z. physikal. Chem.*, 1942, **190**, *A*, 241) found an exchange for the first two of these acids in presence of added alkali, the exchange being restricted to the hydrogen atoms attached to the α-carbon atom. Exclusive α-deuteration has been claimed (Schoenheimer, Rittenberg, and Keston, *J. Amer. Chem. Soc.*, 1937, **59**, 1765) on treatment of palmitic acid with concentrated deuteriosulphuric acid at 100°. On the other hand, Van Heyningen, Rittenberg, and Schoenheimer (*J. Biol. Chem.*, 1938, **125**, 495) found that higher fatty acids (C_6—C_{18}) exchange hydrogen for deuterium readily when heated to 130° in deuterium oxide in presence of alkali and a platinum catalyst. On the basis of the amount of deuterium introduced into the molecule these authors claimed that, under these conditions, many, and possibly all, of the hydrogen atoms were exchanged although equilibrium was not reached after twelve days. It is clear that the enolisation mechanism suggested for the acid–base-catalysed exchange reaction can result in exchange of the hydrogen atoms attached to the α-carbon atom only; such a mechanism cannot lead to exchange of hydrogen atoms attached to other carbon atoms.

Preliminary comparative experiments in the present study have shown that the presence of a platinum catalyst enhances the deuteration of those acids which undergo exchange in the homogeneous reaction and promotes the deuteration of other acids with which the homogeneous reaction does not take place or is too slow for detection. In these experiments, summarized in Table 1, concentrated solutions of the acids in deuterium oxide were shaken at 125—130°, in presence or absence of a platinum catalyst, for 2—10 days. The molar concentration of the acid was, in most cases, about 7—12, while that of the

* Part II, *J.*, 1952, 576.

deuterium oxide varied between 15 and 25, but experiments have also been carried out at concentrations outside the limits of the ranges. For comparison, all the results in Table 1 have been calculated on a common concentration basis of 10M-acid and 10M-deuterium oxide, and for a period of one day, since it was found that, under the conditions employed, equilibrium was not approached in these reactions.

TABLE 1. *Overall deuterium (atom %) introduced per day.*

	Concn. of acid = 10M. Concn. of D_2O = 10M.				
	$CH_3{\cdot}CO_2H$	$C_2H_5{\cdot}CO_2H$	$(CH_3)_3C{\cdot}CO_2H$	$HO{\cdot}CH(CH_3){\cdot}CO_2H$	$CH_3O{\cdot}CH(CH_3){\cdot}CO_2H$
Homogeneous exchange ...	2·9	0·5	← No exchange →		
Pt-catalysed exchange ...	5·4	1·1	0·18	0·58	0·04

As shown for lactic acid in Table 2, the extent of the exchange reaction at the concentrations used was directly proportional to the weight of the platinum catalyst present; from this it may be concluded that the catalyst surface was saturated and that adsorption on the catalyst was a preliminary step in the exchange reaction.

TABLE 2.

Lactic acid (g.)	1·139	1·235	1·239	1·199
D_2O (g.)	1·109	1·109	1·112	1·109
Catalyst (g.)	—	0·025	0·050	0·100
Time (days)	2	2	2	2
Deuterium in lactate (atom %)	0·00	0·85	1·86	4·16

The deuteration of trimethylacetic acid (see Table 1) has demonstrated that hydrogen attached to a carbon atom other than the α-carbon atom can be involved in the exchange reaction catalyzed by platinum, but it is of interest, in the case where both α- and β-hydrogen atoms are available, to attempt to differentiate between the homogeneous and the heterogeneous reaction, and to determine the distribution of deuterium in the deuterated acids from both reactions. Propionic acid, deuterated with and without a catalyst, was degraded by the reactions, $CH_3{\cdot}CH_2{\cdot}CO_2H \longrightarrow CH_3{\cdot}CHBr{\cdot}CO_2H \longrightarrow CH_3{\cdot}CH(OH){\cdot}CO_2H \longrightarrow CH_3{\cdot}CO_2H$, and from determinations of the deuterium content of the propionate and the lactate or the acetate, the distribution of the deuterium between α- and β-positions was readily calculated. Table 3 shows clearly that in presence of the platinum catalyst

TABLE 3. *Deuteration of propionic acid.*

		Deuterium content (atom %)				
		Overall			Propionate	
Expt.	Catalyst	Propionate	Lactate	Acetate	α-Position	β-Position
1	Present	10·41	7·75	—	13·30	8·47
2	Absent	5·93	3·15	—	13·92	0·60
3	Present	20·90	13·66	9·03	38·70	9·03
4	Absent	16·32	9·5	0·48	40·20	0·48

(Expts. 1 and 3) extensive exchange had occurred involving hydrogen atoms attached to both α- and β-carbon atoms, whereas in the absence of platinum (Expts. 2 and 4) the exchange was almost wholly confined to the hydrogen atoms in the α-position. The possibility exists that a loss of deuterium may occur during the oxidative degradation of the acids but support for these results has been provided by mass-spectrometric examination of specimens of methyl propionate prepared from the deuterated propionic acids. For this purpose, consideration of a small region of the cracking patterns of the ester samples is adequate; a fuller account of these and of the cracking patterns of the parent deuterated propionic acids will be reported in due course. As the basis of comparison of the deuterated methyl propionates the large peak at mass 29, corresponding to $C_2H_5^+$ particles, was used as a standard; summarized results of the examination of the relevant portion of the cracking patterns are shown in Table 4.

Comparison of the heights of the peaks for masses 30 and 31, corresponding to $C_2H_4D^+$ and $C_2H_3D_2^+$ respectively, in the case of experiments 1 and 2 shows that only where the

deuteration of the acid had taken place in presence of the platinum catalyst is there evidence of the introduction of two deuterium atoms into the molecule. No definite conclusion regarding α- and β-substitution can be legitimately drawn from this result since

TABLE 4. *Mass-spectrometric examination of methyl propionate.*

		Peak heights				
	Mass no.	29	30	31	32	33
Expt.	Source of acid					
1	Pt-catalysed exchange	100	59·98	64·73	—	—
2	Homogeneous ,, ...	100	46·5	0	—	—
3	Pt-catalysed ,, ...	100	56·4	76·5	47·9	6·8
4	Homogeneous ,, ...	100	123·2	72·9	17·7	4·4

the possibility exists that the two deuterium atoms may both be attached to the same carbon atom and the absence of any dideuterated radical in experiment 2 may be due simply to the relatively small amount (*ca.* 6%) of deuterium in the acid. The esters used in experiments 3 and 4 were prepared from the specimens of the deuterated acids bearing the same numbers in Table 3; and here mass spectrometry showed that, even in the absence of the platinum catalyst, more than one hydrogen atom had been exchanged. The large peak at mass 31 reported for experiment 4 could arise as the result of dideuteration in which both deuterium atoms were attached to the α-carbon atom, since the ester, in this case, was prepared from a specimen of propionic acid containing 16% of deuterium. The greater ease of introduction of further deuterium atoms, which must be attached to the β-carbon atom, when the catalyst is present can be illustrated by expressing the peak heights at the different mass numbers as percentages of the total of all the $C_2H_nD_{5-n}$ species present :

		Abundance (%)				
Mass no.		29	30	31	32	33
Expt. 3	Pt-catalysed exchange	36·3	19·2	24·9	17·2	2·4
Expt. 4	Homogeneous ,, ...	32·8	39·2	21·3	5·6	1·0

A rigid quantitative significance cannot yet be attached to these results owing to the possible existence of an isotope effect, but from these figures approximate values of 20·4 and 15·3 for the overall deuterium contents of the two specimens of propionic acid have been calculated. These values are subject to refinement on more detailed analysis of the mass-spectrometric data, but they are already in agreement with the direct determinations reported in Table 3.

Sufficient evidence to justify consideration of the detailed mechanism of these exchange reactions is not yet available but it is apparent that the platinum-catalysed reaction results in substitution at all carbon atoms.

EXPERIMENTAL

The methods used for the deuteration reactions, preparation of the catalyst, and determination of the deuterium content of the combustion water from the deuterated products have been described in Part I (*J.*, 1952, 572). All combustions were carried out on the silver salts prepared from the acids, after deuteration, by treatment with excess of silver carbonate or silver oxide, so that correction for the deuterium in the carboxyl group was unnecessary. In the case of lactic acid, all samples were treated with a large excess of ordinary water in order to " normalize " the hydroxyl-hydrogen.

Bromination of Propionic Acid.—α-Bromopropionic acid was prepared from the deuterated specimens of propionic acid by the method described by Marvel (*Org. Synth.*, **20**, 106). Final purification was by distillation, the fraction distilling at 100—102°/20 mm. being collected. Yields were 75—86%.

Preparation of Silver Lactate from α-Bromopropionic Acid.—Silver oxide (5·7 g.) was added during 3 hr. to a solution of α-bromopropionic acid (3·4 g.) in water (300 c.c.), the temperature being kept at 80°. The solution was filtered after being kept overnight, and the filtrate heated to 70—80° for 4 hr. with silver carbonate (2 g.). After removal of the excess of silver carbonate by filtration, the solution was evaporated to dryness and the resulting silver lactate dried *in vacuo* over concentrated sulphuric acid (yields, 78—83%).

Oxidation of Silver Lactate.—Silver lactate (2 g.), potassium permanganate (1 g.), and dilute sulphuric acid (5N; 60 c.c.) were steam-distilled until a distillate of 450—500 c.c. had been collected. The distillate was then heated for 1 hr. with silver oxide (1·4 g.) and silver carbonate (0·5 g.), filtered, and concentrated by evaporation, frequent filtration from deposited silver oxide being necessary during the concentration. Evaporation to dryness gave silver acetate in 30—36% yields.

Preparation of Methyl Propionate.—Methyl esters of the deuterated propionic acids for examination in the mass spectrometer were prepared by treatment of the silver salts with methyl iodide, and, for comparison, by the use of diazomethane.

One of us (K. A. M.) is indebted to the Department of Scientific and Industrial Research for the award of a Maintenance Allowance.

UNIVERSITY OF GLASGOW. [*Received, May 6th*, 1953.]

---

695. *The Catalytic Deuteration of Organic Compounds. Part IV.* The Deuteration of Optically Active Lactic Acid.*

By J. BELL, K. A. MACDONALD, and R. I. REED.

The deuteration, at 120—130°, of optically active lactic acid by deuterium oxide in presence of a platinum catalyst has been examined and the extent of deuteration at the α- and the β-carbon atom correlated with the stereochemical changes which occurred simultaneously. The results indicate that the α-substitution of hydrogen by deuterium is, in general, accompanied by inversion. This is supported by a resolution of a partially racemised salt. The substitutions at the α- and the β-carbon atom are shown to be concurrent processes. A mechanism consistent with these observations is discussed.

IN Part III * it was reported that, whereas lactic acid could be deuterated by shaking it with deuterium oxide at 130° in the presence of platinised asbestos, no detectable reaction occurred in the absence of the catalyst. Lactic acid can be readily resolved, and thus this reaction can be used to investigate the stereochemical changes associated with deuteration at a catalytic surface. In two such catalytic deuterations of lactic acid consisting substantially of the lævorotatory form the following results have been obtained.

TABLE 1. *Deuteration of (−)lactic acid.*

	Experiment 1	Experiment 2
(+)-Form present initially (%)	1·48	2·94
,, ,, after deuteration (%) [a]	7·08	8·23
Initial concn. of D in water (atom %) [b]	82·9	82·05
Overall D content of silver lactate (atom %) [c]	4·89	4·51
Concn. of D at α-carbon atom (atom %)	5·52	5·39
,, ,, β-carbon atom (atom %)	6·30	5·71
(+)-Form reqd. for occurrence of Walden inversion (calc.) [d]	7·95	9·12
,, ,, ,, Walden inversion (corr.) [e]	7·30	8·44
,, ,, ,, racemisation (calc.) [f]	4·71	6·03

[a] The assumption is made here that the molecular rotations of $CH_3O{\cdot}CH(CH_3){\cdot}CO_2CH_3$ and $CH_3O{\cdot}CD(CD_3){\cdot}CO_2CH_3$ are not significantly different. [b] Deduced from that of the 99·75% deuterium oxide used by the instantaneous equilibrium, $CH_3{\cdot}CH(OH){\cdot}CO_2H + 2D_2O \rightleftharpoons CH_3{\cdot}CH(OD){\cdot}CO_2D + 2HOD$. [c] Includes the hydroxyl-hydrogen which has been "normalised." [d] Calc. on the assumption that every substitution at the α-carbon atom leads to an inversion of the sign of rotation; β-substitutions are assumed to be without effect on the optical activity. An isotope effect between hydrogen and deuterium has been neglected in the calculation since this would be very small at the relatively high temperature of the reaction. [e] The uncorrected values neglect the small but finite possibility of any molecules undergoing two substitution reactions in the course of the experiment. [f] Based on the symmetrical transition state's having an equal probability of giving D- or L-deuterated forms, no allowance being made for systems where this condition is not met; the present system, however, approximates closely to this condition.

It is apparent from Table 1 that the deuteration reaction proceeds to a substantial extent by a mechanism leading to Walden inversion. Reaction mechanisms of this type

* Part III, preceding paper.

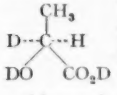
have been extensively studied by Hughes, Ingold, and their co-workers (*J.*, 1937, 1252; 1946, 173) and evidence has been accumulated in the study of homogeneous reaction systems that such inversions occur by a bimolecular reaction mechanism in which the entering group attaches itself to the reactive centre on the side opposite to the group which is expelled. It has also been shown that in general cases of bimolecular substitution of this kind the molecule in the transition state is planar with respect to the active centre and the unreacting groups are distributed around the centre in positions in the plane consistent with the lowest energy configuration. The entering group and that being expelled are coaxial with the reactive centre, the axis so formed being normal to the plane of the rest of the molecule. It is possible, however, that these requirements may not be rigidly met in the case of a molecule reacting on a catalytic surface.

The existence of an inversion in the process excludes from consideration mechanisms involving reversible dehydration and reversible dehydrogenation reactions. The former type clearly cannot effect any deuteration in the α-position unless it is associated with some other concurrent process. Reversible dehydrogenations, involving either αβ-elimination or elimination from the α-hydrogen and the hydroxyl-hydrogen atom, can also be excluded, since the elimination-and-addition reactions could not result in an inversion in the second of these processes and could do so in the first only under certain specified conditions of reaction such as *trans*-elimination followed by *cis*-addition, or the reverse sequence, involving a bimolecular type of reaction at some stage. In either case the presence of deuterium for re-saturation is a condition not fulfilled in these experiments where the bulk of the deuterium was present as the oxide. Under the experimental conditions employed no evidence was found for the presence of acrylic acid or pyruvic acid, although some indication of the latter was obtained at higher temperatures.

Alternative theories which involve the replacement of only one of the hydrogen atoms by the dissociation of a C–H bond as the initial step in the reaction may also be excluded since, if the hydrogen atom is removed and the rest of the molecule attached to the catalyst by the bonding electron or electrons, it is difficult to see why the substitution does not occur with retention of configuration. On the other hand, if the residue becomes detached from the catalyst as a radical which eventually abstracts a deuterium atom either from the catalyst or from the solvent, the reaction should lead to racemisation, as evidence has accumulated that, in general, radicals do not retain their stereochemical configuration even if of very short life (Hey, *Ann. Reports*, 1944, **41**, 189).

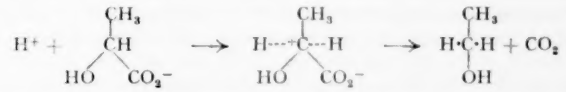
The remaining type of substitution is that requiring synchronous addition and expulsion of the groups and as this appears to be consistent with the experimental evidence available, a general reaction process based on such a mechanism can be described.

According to Laidler (*Discuss. Faraday Soc.*, 1950, 47) the theory of bimolecular surface reactions formulated by Langmuir (*Trans. Faraday Soc.*, 1921, **17**, 621) is more generally applicable than that suggested by Rideal (*Proc. Camb. Phil. Soc.*, 1939, **35**, 130) and a mechanism based on the former theory is considered to be operative in this case, such a mechanism being favoured by the polar nature of the reactants. The high heat of desorption usually associated with this type of mechanism is consistent with the observed rapid sintering of the catalyst in the present experiments. It is suggested, therefore, that this reaction occurs between two particles adsorbed on the catalyst, an equilibrium being set up between deuterium ions in solution and chemisorbed deuterium which may be regarded as bonded to the platinum, the bond being substantially covalent in character so that there is an electron density around the deuterium atom. The lactic acid molecule is also adsorbed on the catalyst, whose function is to lower the activation energy for the formation of the transition state; this will be assisted by the covalent character of the chemisorbed deuterium. The transition state formed between the deuterium and the lactic acid molecule (or the anion) will be essentially of the annexed form and it is clear that expulsion of the hydrogen will lead to inversion. No evidence is available to decide whether the breaking of the D–Pt bond will result in the formation of deuterium ions or atoms and hence no decision as to the nature of the ejected particle can be made.



The presence, among the by-products of the reaction, of a very small amount of ethyl

alcohol is in agreement with the view that the reaction is one between a lactic acid molecule (or anion) and a deuterium atom or ion with considerable covalent character. Ethyl alcohol may arise from a reaction of the type



in which the loss of carbon dioxide is occasioned by charge neutralisation (Brown, *Quart. Reviews*, **1951**, **5**, 131). The amount of alcohol found, corresponding to not more than 0·8% of the reaction, indicates that this process is of almost negligible occurrence.

That the reaction process is not exclusively one of Walden inversion is clear from the extent of inversion and substitution shown in Table 1, from which it has been calculated that the number of substitutions occurring with inversion is approximately six times the number occurring with retention of configuration. Further evidence to this effect has been obtained by a partial resolution, through the morphine salt, of the deuterated lactic acid from Experiment 2, and the assay of the deuterium content in the α- and the β-position. The weight of each fraction being known, in addition to the rotation and the extent of deuteration, the amounts of substitution accompanied by inversion and by retention of configuration have been calculated and are included in Table 2. Little evidence is available to decide whether the second mechanism operating is one leading to racemisation or retention of configuration; it is, however, probable that the alternative reaction occurs by a mechanism similar to that of the main process but with the entering group approaching from the same side of the molecule as that to which the group being expelled is attached. This view is not inconsistent with the adsorption of the lactic acid molecule, which could undergo slight distortion, and replacement of the hydrogen by deuterium chemisorbed deep into the platinum.

TABLE 2.

(−)-Lactic acid (%)	95·49	91·77	46·55
Deuterium in α-position (atom %)	3·30	5·39	30·33
,, β-positions (atom %)	3·40	5·71	36·25
Molecules reacting with inversion (%)	90	85·6	90

The simultaneous deuteration of the α- and the three β-positions is shown clearly in Table 2, but the fact that α- and β-substitutions occur together is not considered as evidence that they are interdependent except in so far as the chemisorption of the molecule brings all four hydrogen atoms into the proximity of the catalyst. For results consistent with the optical rotation and the deuterium content at the two carbon atoms, the substitution processes must occur at least three times for β-substitution, and, for the stereochemical requirements, an odd number of times for each molecule. Little significance can be attached to the observation that three β-substitutions occur for one α-substitution, at least with regard to the relative rates of the two reactions, since a consequence of the Langmuir mechanism is the high energy associated with desorption which is often the rate-controlling process. The fact that the main process in the reaction is that of inversion indicates that, once an inversion has occurred as the result of one substitution at the α-carbon atom, no further reaction takes place at this centre even though this step may be over before desorption occurs. This implies that, once inverted, the molecule is unsuitably placed on the catalyst surface for further reaction, which would appear to be more consistent with the geometry of chemisorbed reacting systems rather than those in which one reacting species is held by long-range van der Waals forces.

The observation that, although the deuteration takes place readily with lactic acid, a similar reaction fails to occur to any significant extent with methoxypropionic acid is explained if such a mechanism involves covalently bonded deuterium by reason of a steric effect in the transition state of the latter acid. Calculations of the steric effects in the molecules of lactic and methoxypropionic acids have been made for the initial state and the transition state and will be discussed in a subsequent communication.

Experimental

Resolution of Optically Inactive Lactic Acid.—The optical enantiomer for use in the exchange reactions was prepared by Purdie and Walker's method (*J.*, 1895, **67**, 617), the criterion of optical purity being the number of molecules of water of crystallisation in the zinc salt (Purdie, *J.*, 1893, **63**, 1143). The zinc lactate was converted into lactic acid by passing hydrogen sulphide into an aqueous solution of the salt and filtering off the zinc sulphide repeatedly until no further precipitate was obtained. The filtered solution was evaporated to small bulk and extracted with ether in a continuous extractor for 16 hr. The ethereal layer was dried (Na_2SO_4), the ether removed, and the lactic acid distilled, the fraction, b. p. 79—81/0·1 mm., being collected. On shaking, the distillate, subsequently found to contain 98·5% of the lævorotatory form, set to a white crystalline mass, m. p. 49·5°. A second sample, prepared by the same method (97·1% of the lævorotatory form), had m. p. 54° (Found : C, 39·8; H, 6·7. Calc. for $C_3H_6O_3$: C, 40·0; H, 6·7%).

The deuterated lactic acid was resolved by means of the morphine salt. Lactic acid (20 g.) in solution from the deuteration reaction was diluted to 200 ml. with water and refluxed for 3 hr. to hydrolyse any lactide. Morphine (63·5 g.) was added, and, on cooling, a copious precipitate of morphine lactate settled out and was filtered off. Four further crops were obtained by concentration. The residue (6 g.) set to a syrup. Lactic acid was recovered by addition of ammonia, in excess, to aqueous solutions of the morphine lactate, removal of the morphine by filtration, boiling to remove the excess of ammonia, decomposition of the ammonium lactate with dilute sulphuric acid, and extraction with ether.

Silver Lactate.—Active lactic acid was refluxed with water for 3 hr. to hydrolyse lactide. The calculated quantity of silver oxide was gradually added to the boiling solution which was boiled for a further 5 min. after all the silver oxide had been added, and then evaporated to small bulk. After filtration from small quantities of silver oxide, the solution was cooled in ice and the precipitated silver lactate filtered off. This process was repeated until the final volume of the solution was about 2 ml., from which the remaining silver lactate was precipitated by the addition of alcohol (yield 83—84%). Although the later fractions contained some silver oxide it was considered advisable to include these in order to assay a representative sample.

Methyl Lactate.—Lactic acid was converted into methyl lactate by Walker's method (*J.*, 1895, **67**, 916), the fraction, b. p. 58—60°, being collected.

Methyl Methoxypropionate.—This was prepared from methyl lactate by Purdie and Irvine's method (*J.*, 1899, **75**, 485), the crude product being fractionated at atmospheric pressure, b. p. 130—131°.

Methoxypropionic Acid.—The acid, prepared from the methyl ester as described by Freudenberg (*Ber.*, 1927, **60**, 2452), had b. p. 85—90°/9 mm.

Rotations.—These were measured at 20° in a 1-dm. tube, for the sodium *D* line. Lactic acid specimens were converted into methyl methoxypropionate, and the activity of the acid determined by measurement of the rotation of this ester, the value for the pure ester, taken as standard, being $[\alpha]_D^{20}$ +95·53° (Purdie and Irvine, *loc. cit.*).

Oxidations.—Several methods were used for converting the lactic acid and its derived esters into acetic acid for deuterium assay. (*a*) *Lactic acid to acetic acid.* The lactic acid was oxidised by refluxing it with excess of potassium permanganate in 2N-sulphuric acid for ½—1 hr. The manganese dioxide was filtered off and the filtrate steam-distilled, the distillate being treated with silver oxide by the method described above for the preparation of silver lactate. The silver acetate so obtained was dried *in vacuo* over sulphuric acid before assay. By using information previously obtained (Part I, *J.*, 1952, 572) it was possible to show that under these conditions the loss of deuterium from the acetic acid was less than 0·5% of the amount estimated.

(b) *Methyl methoxypropionate to acetic acid.* (i) *Direct.* Refluxing the ester with the calculated quantity of potassium permanganate in 2N-sulphuric acid, removal of the manganese dioxide by filtration, and steam-distillation yielded acetic acid which was converted into silver acetate and assayed for deuterium. This method was discarded since a check showed that the deuterium content of the derived acetic acid was 10% below that of the methyl group of the methoxypropionic acid. (ii) *Indirect.* This method gave satisfactory results and was adopted. The ester (4 g.) was refluxed with constant-boiling hydriodic acid (30 g.) for 1 hr. at 140°, the cooled mixture being then diluted to 100 ml. with water and extracted with ether. Free iodine was removed by shaking with sodium metabisulphite, and the ethereal extract dried (Na_2SO_4). Part of the residue after removal of the ether was converted into the silver salt and analysed

(Found: C, 21·9; H, 3·3; Ag, 51·4. Calc. for $C_4H_7O_3Ag$: C, 22·8; H, 3·3; Ag, 51·2%). The silver methoxypropionate, or the free acid, was converted into acetic acid by permanganate oxidation, followed by steam-distillation, and silver acetate prepared by the standard procedure (Found: C, 14·1; H, 1·7; Ag, 64·7. Calc. for $C_2H_3O_2Ag$: C, 14·4; H, 1·8; Ag, 64·7%).

Deuterations.—The active lactic acid, heavy water, and platinum black catalyst on an asbestos support, were weighed into Pyrex tubes in quantities shown in the following Table.

Experiment	1	2
Lactic acid (g.)	16·80	20·08
D_2O (99·78%) (g.)	18·37	20·07
Pt catalyst * (g.)	1·50	1·80
Duration of heating (hr.)	46	44

* Pt (30%) on asbestos; figures give wt. of catalyst plus support.

The tubes were cooled in liquid air, evacuated, sealed, and shaken at 120—130°. The resultant mixture was filtered from the catalyst, and the heavy water recovered by vacuum-distillation at 40°. For deuterium assay, one small portion of the lactic acid was converted into silver lactate and another into silver acetate by the methods outlined above. Further amounts were converted into methyl methoxpropionate for measurement of the optical rotation, and in Experiment 2 a portion of the deuterated lactic acid was partially resolved by means of morphine. All samples of lactic acid were treated with a large excess of ordinary water at some stage in the treatment to normalise the hydrogen atoms of the hydroxyl and the carboxyl group.

By-products.—The aqueous (D_2O) solution obtained by vacuum-distillation was made alkaline with sodium hydroxide and fractionally distilled, only a few ml. of distillate being collected. A portion of this distillate was dried (Na_2SO_4), re-distilled at the temperature of an acetone–carbon dioxide freezing mixture, and examined in a mass spectrometer. The highest peak recorded was one at mass 46, with which were associated peaks at masses 29, 17, and 15, the last two being less prominent. In addition, a small peak at mass 44 and a fairly large peak at mass 28 were obtained. Some of these mass numbers could be derived from ethyl alcohol (46) giving rise, by breakdown, to ethyl (29), hydroxyl (17), and methyl (15) radicals.

The distillate gave a positive iodoform reaction, and on the assumption that this was due solely to ethyl alcohol, the amount of the latter formed was 4·5 mg., corresponding to about 0·8% of the total reaction. A further portion gave a slight precipitate of a 2 : 4-dinitrophenylhydrazone indicating the presence of an aldehyde or ketone, probably acetaldehyde, since the absence of a peak above mass 46, in the mass spectrometer examination, excludes acetone (58). The presence of acetaldehyde could account for the peak at mass 28 as carbon monoxide produced by the breaking up of the molecule.

Microanalyses were made by Mr. J. M. L. Cameron and Miss R. H. Kennaway, and deuterium assays by Mr. A. Macdonald. One of us (K. A. M.) acknowledges his indebtedness to the Department of Scientific and Industrial Research for a Maintenance Allowance.

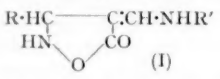
University of Glasgow. [*Received, May 6th,* 1953.]

696. iso*Oxazolones. Part IV.* The Bromination of Arylaminomethyleneisooxazolidones. A New Selective Anion-precipitant.*

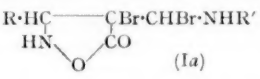
By G. Shaw.

The reaction of 3-methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one (I; R = Me, R′ = *p*-tolyl) with bromine gave the hydrobromide of 3-amino-1 : 2-dibromo-1-*p*-toluidinobut-2-ene (II*a*) which was readily dehydrobrominated to 3-amino-2-bromo-1-*p*-tolyliminobut-2-ene (III*a*). Similar compounds were obtained from (I; R = Me, R′ = Ph) but not from (I; R = Ph, R′ = *p*-tolyl). With the potassium salts of a number of simple acids, the hydrobromide of (III*a*) gave insoluble crystalline salts in dilute, neutral and acidic solution. The properties of some of the salts were examined and the precipitant compared with known anion-precipitants, including nitron which was in general more sensitive but less selective.

During an investigation of arylaminomethylene*iso*oxazolidones (*J.*, 1951, 1017; 1952, 3428), it was observed that addition of bromine to a solution of 3-methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one (I; R = Me, R′ = *p*-tolyl) in acetic acid gave carbon dioxide and an immediate orange-yellow precipitate. With care, a compound (*A*) could be crystallised from acetic acid but when its solution in that solvent was boiled for a short time a second substance (*B*) was obtained. Hydrolysis of *A* or *B* with dilute hydrochloric acid gave ammonia, *p*-toluidine, and bromoacetone, and this, in conjunction with analytical data, indicated that *A* and *B* are hydrobromides of the bases (II*a*) and (III*a*) respectively the reaction *A* ⟶ *B* being a dehydrobromination. That the compounds were salts was confirmed by treatment with sodium hydroxide solution which in each case gave the same base, namely (III*a*). Hydrolysis of the impure precipitate *A* also gave, in addition to the



(I)



(Ia)

$NH_2 \cdot CMe{:}CBr \cdot CHBr \cdot NHR$

(II*a*; R = *p*-tolyl)

(II*b*; R = Ph)

[II*c*; R = 2 : 6-dibromo-*p*-tolyl (Me = 4)]

$NH_2 \cdot CMe{:}CBr \cdot CH{:}NR$

(III*a*; R = *p*-tolyl)

(III*b*; R = Ph)

above-mentioned compounds, a small amount of 2 : 6-dibromo-*p*-toluidine which suggested the presence, in the mixture, of (II*c*) although this could not be isolated, and at the same time indicated a source of hydrogen bromide for the main reaction, in which (I*a*) would be an intermediate.

An aqueous solution of the sparingly soluble hydrobromide of (III*a*) gave crystalline precipitates in dilute, neutral and acidic solution with a number of anions, including nitrate, iodide, perchlorate, chromate, thiocyanate, and picrate, but not with chloride, nitrite, sulphate, phosphate, acetate, or oxalate. Organic bases which form water-insoluble salts with simple anions are relatively uncommon and include nitron (cf. Cope and Barab, *J. Amer. Chem. Soc.*, 1917, **39**, 504), di-(α-naphthylmethyl)amine (Rupe and Becherer, *Helv. Chim. Acta*, 1923, **6**, 674, 885; Konek, *Z. anal. Chem.*, 1934, **97**, 416), and 2-diethylamino-1-phenethyl *p*-nitrobenzoate (Marvel and du Vigneaud, *J. Amer. Chem. Soc.*, 1924, **46**, 2095, 2661). Some comparative approximate minimum anion concentrations required for precipitation are given in the Table. Our hydrobromide and the *p*-nitrobenzoate are more selective in their action, but much less sensitive, than nitron.

The precipitate from the reaction between potassium iodide and the hydrobromide of (III*a*) contained potassium and is apparently a double salt of the reactants. It had approximately the same solubility as the hydriodide of (III*a*), and was precipitated as

* Part III, *J.*, 1952, 3428.

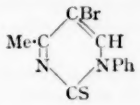
brownish-yellow needles at anion concentrations >0·1N but as a deep blue-black form in more dilute solution; the latter, when heated, reverted to the brown modification.

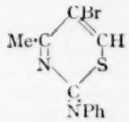
The thiocyanate of (III*a*) could not be isomerised to the corresponding thiourea; an ethanolic solution of the salt, however, when left at room temperature for several days gave a small amount of a bright yellow substance to which no simple structure could be

Minimum anion concentration (N) *for precipitation at* 20°.

Anion	(III*a*)	*p*-Nitrobenzoate	Nitron	Anion	(III*a*)	*p*-Nitrobenzoate	Nitron
NO_3	0·01	0·005	0·0001	I	0·0005	0·01	0·0005
ClO_4	0·0025	0·0025	0·0001	CNS	0·025	—	0·001

assigned. The reaction between (III*a*) and phenyl *iso*thiocyanate gave a similar yellow compound, analysis of which, however, indicated it to be derived from the expected thiourea by loss of *p*-toluidine; it may be formulated as the thiopyrimidone (IV), rather than (V) since it failed to give aniline when boiled with dilute hydrochloric acid.

(IV) 



(V)

Bromination of (I; R = Me, R′ = Ph) gave, in a similar manner, salts of (II*b*) and (III*b*), and the latter product formed salts which were slightly more soluble than those of (III*a*). Treatment of (I; R = Ph, R′ = *p*-tolyl) with bromine in acetic acid, in a single attempt to obtain a more sensitive compound, failed to yield a precipitate or any obvious signs of reaction even after several days at room temperature; when the solution was warmed, a vigorous reaction occurred, but only 2 : 6-dibromo-*p*-toluidine (Me = 4) was isolated.

Experimental

3-*Amino*-1 : 2-*dibromo*-1-p-*toluidinobut*-2-*ene* (II*a*).—3-Methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one (5 g.) in acetic acid (100 ml.) was treated with a solution of bromine (4 ml.) in acetic acid (25 ml.). Carbon dioxide was liberated (barium hydroxide solution) and an immediate orange-yellow precipitate appeared; **3-*amino*-1 : 2-*dibromo*-1-p-*toluidinobut*-2-*ene hydrobromide*** (8 g.) separated from warm acetic acid (the solution must not be boiled) as orange-yellow prisms, m. p. 238° (decomp.) (Found: C, 32·45; H, 3·5; N, 6·75. $C_{11}H_{14}N_2Br_2$,HBr requires C, 31·8; H, 3·65; N, 6·75%); the high value for carbon may be due to the presence of a small amount of the dehydrobrominated material.

3-*Amino*-2-*bromo*-1-p-*tolyliminobut*-2-*ene* (III*a*).—The dibromo-compound (8 g.) was boiled with acetic acid (400 ml.) until a clear solution resulted; when cooled, the solution deposited red crystals (4·5 g.); **3-*amino*-2-*bromo*-1-p-*tolyliminobut*-2-*ene hydrobromide*** separated from acetic acid as reddish-orange cruciform prisms or from water as yellow prisms, m. p. 198° (decomp.) (Found: C, 39·2; H, 4·15; N, 8·45. $C_{11}H_{13}N_2Br$,HBr requires C, 39·5; H, 4·2; N, 8·4%); a further quantity (1 g.) was obtained on concentration. The hydrobromide (1 g.) was dissolved in water (150 ml.), and the solution made alkaline with 2N-sodium hydroxide, to give a cream precipitate; **3-*amino*-2-*bromo*-1-p-*tolyliminobut*-2-*ene*** (0·6 g.) separated from light petroleum as very pale yellow plates, m. p. 98° (Found: C, 52·15; H, 5·0; N, 11·1. $C_{11}H_{13}N_2Br$ requires C, 52·2; H, 5·2; N, 11·05%). The hydrobromide (1 g.) was boiled under reflux with 2N-hydrochloric acid (20 ml.) for 30 min. and the resulting clear solution distilled until the volume was about 10 ml. The distillate was strongly lachrymatory and with an excess of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid gave, overnight, bromoacetone 2 : 4-dinitrophenylhydrazone, yellow needles (from ethanol), m. p. and mixed m. p. 123°. When the residual hydrolysis solution was basified with sodium hydroxide solution there was an odour of ammonia; extraction with ether gave a base characterised as the benzoyl derivative, m. p. 157—158° not depressed when mixed with *N*-benzoyl-*p*-toluidine. A similar hydrolysis carried out on the first-mentioned bromination product gave, in addition to *p*-toluidine, ammonia, and bromoacetone, a small amount of solid which appeared in the distillate and crystallised from ethanol–water as colourless needles, m. p. 69° (Found: C, 31·8; H, 2·75; N, 5·3. Calc. for

$C_7H_7NBr_2$: C, 31·7; H, 2·65; N, 5·3%), not depressed on admixture with 2 : 6-dibromo-*p*-toluidine.

3-*Amino*-1 : 2-*dibromo*-1-*anilinobut*-2-*ene* (II*b*).—4-Anilinomethylene-3-methyl*iso*oxazolid-5-one (2·5 g.) in acetic acid (50 ml.) was treated with bromine (2 ml.) in acetic acid (15 ml.); an immediate yellow microcrystalline precipitate was filtered off rapidly; the filtrate when kept for a short time deposited yellow prisms (3 g.), m. p. 200° (decomp.). The compound could not be recrystallised satisfactorily but was probably 3-*amino*-1-*anilino*-1 : 2-*dibromobut*-2-*ene acetate* (Found : C, 37·95; H, 4·15; N, 7·45. $C_{10}H_{12}N_2Br_2,C_2H_4O_2$ requires C, 37·9; H, 4·25; N, 7·35%).

3-*Amino*-2-*bromo*-1-*phenyliminobut*-2-*ene* (III*b*).—The acetate (1 g.), when boiled with acetic acid, similarly gave 3-*amino*-2-*bromo*-1-*phenyliminobut*-2-*ene hydrobromide* (0·3 g.) as yellow prisms (from acetic acid), m. p. 184—185° (decomp.) (Found : N, 8·8. $C_{10}H_{11}N_2Br,HBr$ requires N, 8·75%). Hydrolysis of the hydrobromide or the acetate with hydrochloric acid gave ammonia, aniline, and bromoacetone.

Bromination of 3-*Phenyl*-4-p-*toluidinomethylene*iso*oxazolid*-5-*one*.—The *iso*oxazolidone (1 g.) and bromine (0·5 ml.) were mixed in acetic acid; no obvious reaction occurred when the mixture was left at room temperature for 3 days. Heating caused a vigorous reaction, with liberation of hydrogen bromide; the clear solution obtained when treated with excess of water gave 2 : 6-dibromo-*p*-toluidine, m. p. and mixed m. p. 68—69°.

Salts of 3-*Amino*-2-*bromo*-1-p-*tolyliminobut*-2-*ene*.—A saturated solution of the hydrobromide with 0·1N-solutions of the potassium salts of a number of acids gave the results recorded. The *nitrate monohydrate* separated from water as pale yellow needles, m. p. 205° (decomp.) (Found : C, 39·75; H, 4·55; N, 12·3. $C_{11}H_{13}N_2Br,HNO_3,H_2O$ requires C, 39·5; H, 4·2; N, 12·55%), the *perchlorate* as cream prisms (from water), m. p. 245° (decomp.) (Found : C, 37·35; H, 3·9; N, 8·1. $C_{11}H_{13}N_2Br,HClO_4$ requires C, 37·6; H, 4·0; N, 8·0%), and the *thiocyanate* as pale yellow needles (from water), m. p. 160° (decomp.) (Found : C, 46·0; H, 4·4; N, 13·4. $C_{11}H_{13}N_2Br,HCNS$ requires C, 46·15; H, 4·5; N, 13·45%). The salt gave a blood-red colour with ferric chloride. The product of reaction of the hydrobromide and potassium iodide was obtained as brown needles from 0·1N-solutions and as deep blue hair-like needles from more dilute solution; the blue substance was converted into the brown by heating it at 100° for 10 min. The *substance* separated from ethanol–water as brownish-yellow needles, m. p. 185° (decomp.) (Found : C, 26·95; H, 2·8; N, 5·55. $C_{11}H_{13}N_2Br,HBr,KI$ requires C, 26·4; H, 2·8; N, 5·6%). This (0·05 g.) was suspended in ethanol (1 ml.), and 2N-sodium hydroxide (1 drop) was added to give a clear solution from which excess of water precipitated 3-amino-2-bromo-1-*p*-tolyliminobut-2-ene (0·02 g.), m. p. and mixed m. p. 97—98°. The *iodide hemi-hydrate* (from the hydrobromide and hydriodic acid or sodium iodide) separated from water as yellow needles, m. p. 183° (decomp.) (Found : C, 33·8; H, 3·75; N, 7·3. $C_{11}H_{13}N_2Br,HI,\frac{1}{2}H_2O$ requires C, 33·8; H, 3·85; N, 7·2%).

Attempted Rearrangement of the Thiocyanate.—The thiocyanate (0·5 g.) in ethanol (5 ml.), left at room temperature for 2 days, gave a bright yellow solution; addition of water precipitated a *substance* (0·1 g.) which separated from ethanol–water as yellow needles, m. p. 185° (decomp.) (Found : C, 35·25; H, 3·9; N, 7·55%).

Anion :		Ppt.		Anion :		Ppt.	
Nature	N	Neutral	Plus 1 drop of N-HCl	Nature	N	Neutral	Plus 1 drop of N-HCl
NO_3	0·1	Immediate	Immediate	ClO_4	0·01	5 Min.	15 Min.
NO_3	0·025	10 Min.	1 Hr.	ClO_4	0·0025	Overnight	Overnight
NO_3	0·01	Overnight	None	ClO_4	0·001	None (cloudy)	None
I	0·01	Immediate	Immediate	CNS	0·1	Immediate	Immediate
I	0·001	2 Hr.	2 Hr.	CNS	0·025	Overnight	Overnight
I	0·0005	Overnight	Overnight	CNS	0·01	None	None
I	0·0001	None (cloudy)	None				

Reaction of (III*a*) *with Phenyl* iso*Thiocyanate*.—The base (0·5 g.) and phenyl *iso*thiocyanate (0·5 g.) were mixed in ether (10 ml.) and left overnight. A crystalline solid separated, together with a red gum. The solid (0·1 g.) crystallised from benzene–light petroleum as yellow prisms, m. p. 140° (decomp. with resolidification to a brown material, m. p. 300°) and may be 5-*bromo*-4-*methyl*-1-*phenyl*-2-*thiopyrimidone* (Found : C, 46·5; H, 3·1; N, 9·5. $C_{11}H_9N_2BrS$ requires C, 46·95; H, 3·2; N, 9·95%). It was soluble in concentrated mineral acid solutions and was recovered unchanged after being boiled with 5N-hydrochloric acid for a few min.

Sensitivity of the Anion Tests.—The tests were carried out by treating 5 ml. of the anion solution (K^+ or a common cation) with 0·5 ml. of a saturated solution of the hydrobromide of (III*a*) at 20°; the rate of precipitation and the sensitivity were increased by cooling the solutions.

The author thanks Dr. E. Challen for the semimicro-analyses.

THE UNIVERSITY OF TECHNOLOGY,
SYDNEY, N.S.W. AUSTRALIA.

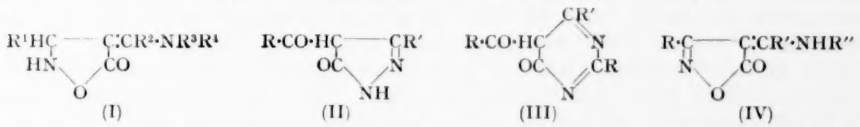
[*Received, June 1st,* 1953.]

697. iso*Oxazolones. Part V.* Arylaminoalkyl(or aryl)idene-*iso*oxazolones and -*iso*oxazolidones.*

By E. MANSBERG and G. SHAW.

The reaction of *NN'*-diphenylacetamidine and benzamidine with 3-phenyl-*iso*oxazol-5-one gave the *iso*oxazolones (IV; R = R'' = Ph, R' = Me and Ph), and similar products (V; R = Me and Ph) were obtained from 3-methyl-1-phenylpyrazol-5-one. Hydrolysis, hydrogenation, and methylation of the products have been studied.

THE reaction of arylaminomethylene*iso*oxazolidones (I; R^2 = H) with hydrazines and aromatic amidines has been shown (Part III, *J.*, 1952, 3428) to give acyl-pyrazolones and -pyrimidones (respectively II and III; R' = H). This has now been extended in an attempt to prepare other pyrazolones and pyrimidones; syntheses were required of arylaminoalkyl(or aryl)idene-*iso*oxazolones (IV; R' = alkyl, etc.) and -*iso*oxazolidones (I; R^2 = alkyl, etc.) and of *N*-alkyl- or *N*-aryl-*iso*oxazolidones (I; R^3 and R^4 = alkyl or aryl), which could not undergo the base-catalysed rearrangement characteristic of (I; R^2 = R^3 = H, R^4 = aryl), a limiting factor in the preparation of the pyrimidines.



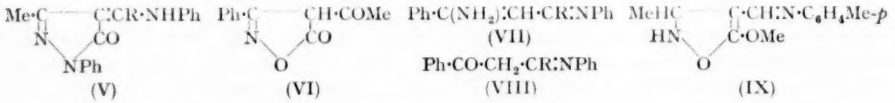
Equimolar parts of 3-phenyl*iso*oxazol-5-one and *NN'*-diphenylacetamidine, kept at 120—130° for 1 hour, gave smoothly the *iso*oxazolone (IV; R = R'' = Ph, R' = Me). The reaction, analogous to that of *NN'*-diaryl-formamidines with reactive methylene groups, namely, $>CH_2 + Ar{\cdot}N{:}CR{\cdot}NHAr \longrightarrow C{:}CR{\cdot}NHAr + ArNH_2$, does not appear to have been recorded previously; its generality was confirmed by the preparation, in a similar manner, of (IV; R = R' = R'' = Ph) from the phenyl*iso*oxazolone and *NN'*-diphenylbenzamidine, and of the compounds (V; R = Me and Ph) from 3-methyl-1-phenylpyrazol-5-one and the appropriate amidines. Ethyl acetoacetate and *NN'*-diphenylacetamidine reacted, however, with difficulty, to give a high-melting compound to which no simple structure could be assigned. The amidines failed to remove the benzylidene group in 4-benzylidene-3-methyl*iso*oxazol-5-one below 150°, and above this temperature decomposition resulted. Similar experiments with (*a*) methyl-*NN'*-diphenyl*iso*thiourea, *NN'*-diphenylguanidine, and *NN'N''*-triphenylguanidine and (*b*) phenyl*iso*oxazolone were also unsuccessful, the first-mentioned compound reacting with loss of methanethiol, and the others with decomposition.

Reaction of the *iso*oxazolone (IV; R = R'' = Ph, R' = Me) with boiling dilute alkali, was similar to that of the *iso*oxazolones (IV; R' = H) (Cook and Shaw, *J.*, 1952, 4466), and gave the ketone (VI), which was converted back into (IV; R = R'' = Ph, R' = Me) by hot aniline. The *iso*oxazolone (IV; R = R' = R'' = Ph), however, was remarkably resistant and was recovered unchanged from 2N-sodium hydroxide solution after 4 hr.' boiling; continued boiling with aqueous-alcoholic hydrogen chloride opened the *iso*oxazol-

* Part IV, preceding paper.

one ring, to form dibenzoylmethane; it is interesting that 4-anilinomethylene-3-methyl-1-phenylpyrazol-5-one (Dains and Brown, *J. Amer. Chem. Soc.*, 1909, **31**, 1148) was not hydrolysed by alkali, also that recovery of the *iso*oxazolone (IV; R = R′ = R″ = Ph) from alkaline solution by acidification was attended by the precipitation of a bright yellow solid [possibly an enol ·C(OH):C·CR′:NR″] which after a few seconds had changed to the colourless *iso*oxazolone.

Hydrogenation of the *iso*oxazolone (IV; R = R″ = Ph, R′ = Me) in ethanol at a platinum catalyst gave the *iso*oxazolidone (I; R^1 = R^3 = Ph, R^2 = Me, R^4 = H) which was readily hydrolysed to the anil (VIII; R = Me) or benzoylacetone. The *iso*oxazolidone with hydrazine readily gave the pyrazolone (II; R = Ph, R′ = Me) in rather low yield, but with aromatic and aliphatic amidines or with sodium hydroxide the base (VII; R = Me) was obtained almost quantitatively; this structure followed from acid hydrolysis to benzoylacetone, ammonia, and aniline. Hydrogenation of the *iso*oxazolone (IV; R = R′ = R″ = Ph) in ethanol or ethyl acetate gave the base (VII; R = Ph) exclusively and this furnished ammonia, aniline, and dibenzoylmethane on hydrolysis. These experiments suggest that the introduction of increasingly large substituents R^2 in (I) is accompanied by an increased tendency of the *iso*oxazolidone to rearrange, presumably to the acid $RC(NH_2)$:$CH(CO_2H)$·CR:NR, and thence to the base (VII).



Possible routes to the required *iso*oxazolidones (I; R^3 = R^4 = alkyl or aryl) included the condensation of *N*-alkyl-*NN*′-diarylformamidines with an *iso*oxazolone, or alkylation of the available *iso*oxazolones (IV; R = H) and hydrogenation of the products, or alkylation of *iso*oxazolidones (I; R^2 = R^3 = H, R^4 = aryl). *N*-Methyl-*NN*′-di-*p*-tolylformamidine was prepared, in rather poor yield, from *NN*′-di-*p*-tolylformamidine and methyl iodide (Lander, *J.*, 1904, **85**, 996); an attempt to prepare the amidine by desulphurisation of *N*-methyl-*NN*′-di-*p*-tolylthiourea with Raney nickel in benzene failed, although we have frequently used this method successfully for the preparation of *NN*′-diarlyformamidines from corresponding thioureas. The *N*-methylformamidine reacted with 3-phenyl*iso*oxazol-5-one but the product was an intractable gum which did not have the physical properties expected of the required *iso*oxazolone. Attempted methylation of 3-methyl-4-*p*-toluidinomethylene*iso*oxazol-5-one with methyl iodide or methyl sulphate, alone or in the presence of a base, or with diazomethane, was also unsuccessful. 3-Methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one (I; R^1 = Me, R^2 = R^3 = H, R^4 = *p*-tolyl), however, reacted slowly with diazomethane, to give a basic compound with the required molecular formula; hydrolysis of this substance with hydrochloric acid gave ammonia, *p*-toluidine, and acetone, indicating that it was the methoxy*iso*oxazoline (IX); the *iso*oxazoline was readily hydrogenated to a substance, possibly $C_{11}H_{15}O_4N$, to which no simple structure could be assigned.

Experimental.

4-1′-*Anilinoethylidene*-3-*phenyl*isoo*xazol*-5-*one* (IV; R = R″ = Ph, R′ = Me).—A finely ground mixture of 3-phenyl*iso*oxazol-5-one (2·7 g.) and *NN*′-diphenylacetamidine (3·5 g.) was kept at 120—130° (bath) for 1 hr., then cooled. The hard red glass dissolved in boiling ethanol (40 ml.); when cooled, the solution gave crystalline 4-1′-*anilinoethylidene*-3-*phenyl*isoo*xazol*-5-*one* (1·5 g.) which recrystallised from ethanol as plates, m. p. 184—185° (Found: C, 73·15; H, 5·1; N, 10·25. $C_{17}H_{14}O_2N_2$ requires C, 73·35; H, 5·05; N, 10·05%). A further quantity (0·5 g.) separated from the filtrate overnight.

4-1′-*Anilinobenzylidene*-3-*phenyl*isoo*xazol*-5-*one* (IV; R = R′ = R″ = Ph).—3-Phenyl*iso*oxazol-5-one (3 g.) and *NN*′-diphenylbenzamidine (5 g.) at 140—150° (bath) (1 hr.) gave 4-1′-*anilinobenzylidene*-3-*phenyl*isoo*xazol*-5-*one* (2·5 g.), plates (from ethanol), m. p. 238° (decomp.) (Found: C, 77·5; H, 4·6; N, 8·3. $C_{22}H_{16}O_2N_2$ requires C, 77·65; H, 4·75; N, 8·25%).

4-1′-*Anilinoethylidene*-5-*methyl*-2-*phenylpyrazol*-3-*one* (V; R = Me).—5-Methyl-2-phenyl-

pyrazol-3-one (0·8 g.) and *NN'*-diphenylacetamidine (1 g.) at 160° (1 hr.) gave the *pyrazolone* (1 g.), yellow laths (from ethanol), m. p. 184—185° (Found: C, 73·9; H, 5·75; N, 14·3. $C_{18}H_{17}ON_3$ requires C, 74·2; H, 5·9; N, 14·4%).

4-1'-*Anilinobenzylidene*-5-*methyl*-2-*phenylpyrazol*-3-*one* (V; R = Ph).—The *pyrazolone* was obtained similarly as yellow prisms (from ethanol), m. p. 161—162° (Found: C, 78·1; H, 5·2; N, 11·8. $C_{23}H_{19}ON_3$ requires C, 78·15; H, 5·4; N, 11·9%).

Reaction of NN'-Diphenylacetamidine with Ethyl Acetoacetate.—Ethyl acetoacetate (3·25 g.) and *NN'*-diphenylacetamidine (5·25 g.) were heated together at 200° (bath) for 1 hr. (little or no reaction occurred below this temperature); the cooled melt with excess of ether gave a *substance* (0·5 g.) which separated from pyridine as pale yellow needles, m. p. 296—300° (decomp.) (Found: C, 73·6; H, 4·8; N, 11·1%).

4-*Acetyl*-3-*phenyl*isoo*xazol*-5-*one* (VI).—A suspension of 4-1'-anilinoethylidene-3-phenyl*iso*oxazol-5-one (1 g.) in 2% sodium carbonate solution was distilled until a small volume (*ca.* 15 ml.) remained; the *iso*oxazolone slowly dissolved and aniline appeared in the distillate. Acidification of the ice-cold residual solution gave 4-*acetyl*-3-*phenyl*isoo*xazol*-5-*one* (0·55 g.) which crystallised from water or benzene–light petroleum as laths, m. p. 136—137° (Found: C, 65·45; H, 4·6; N, 7·1. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·45; N, 6·9%). The ketone gave a red colour and precipitate with ferric chloride in aqueous alcohol. The 2:4-*dinitrophenylhydrazone* separated from methanol as pale yellow laths, m. p. 212° (decomp.) (Found: C, 53·1; H, 3·3; N, 18·05. $C_{17}H_{13}O_6N_6$ requires C, 53·25; H, 3·4; N, 18·25%), and the *phenylhydrazone* from methanol–water as colourless needles, m. p. 167° (Found: C, 69·4; H, 5·15; N, 14·35. $C_{17}H_{15}O_2N_3$ requires C, 69·6; H, 5·15; N, 14·35%). The ketone (0·1 g.) and aniline (0·1 g.), heated together at 150° (bath) for 10 min. and then acidified, gave 4-1'-anilinoethylidene-3-phenyl*iso*oxazol-5-one (0·1 g.), m. p. 185° alone or mixed with the material prepared as above.

4-1'-*Anilinoethylidene*-3-*phenyl*isoo*xazolid*-5-*one* (I; $R^1 = R^3 = Ph$, $R^2 = Me$, $R^4 = H$).—A suspension of 4-1'-anilinoethylidene-3-phenyl*iso*oxazol-5-one (1 g.) in ethanol (50 ml.) was hydrogenated over platinum until 1 mol. of hydrogen had been absorbed (2 hr.), a clear solution being obtained; evaporation *in vacuo* gave a crystalline residue; 4-1'-*anilinoethylidene*-3-*phenyl*isoo*xazolid*-5-*one* (0·8 g.) separated from ethyl acetate as pale yellow needles, m. p. 143—144° (decomp.) (Found: C, 73·0; H, 5·9; N, 10·25. $C_{17}H_{16}O_2N_2$ requires C, 72·85; H, 5·75; N, 10·0%). The *iso*oxazolidone (0·1 g.) dissolved in warm N-hydrochloric acid (20 ml.) to a clear solution which after 1 hr. had deposited a crystalline solid; 1-*benzoyl*-2-*phenyliminopropane* (0·05 g.) separated from light petroleum as pale yellow plates, m. p. 112° (Found: N, 5·85. $C_{16}H_{15}ON$ requires N, 5·9%). The *iso*oxazolidone (0·5 g.) was boiled with N-hydrochloric acid (10 ml.) for 10 min., to give an emulsion which when cooled gave benzoylacetone (0·3 g.) as colourless prisms (from water), m. p. and mixed m. p. 61—62°. Basification of the filtrate with sodium hydroxide solution gave ammonia and aniline.

4-*Acetyl*-5-*methylpyrazol*-3-*one* (II; R = Ph, R' = Me).—4-1'-Anilinoethylidene-3-phenyl-*iso*oxazolid-5-one (0·28 g.) was added to a solution prepared from hydrazine sulphate (0·13 g.), water (1 ml.), ethanol (10 ml.), and sodium (0·05 g.), and the mixture was boiled under reflux for 15 min.; ammonia was freely evolved and some ammonium carbonate sublimed into the condenser. The solution was evaporated *in vacuo* to a small volume, and water (5 ml.) added to precipitate a solid; the solid was dissolved in N-sodium hydroxide (2 ml.), the solution filtered from a small residue, the filtrate acidified with hydrochloric acid, and the precipitated 4-*acetyl*-5-*methylpyrazol*-3-*one* (0·05 g.) crystallised from ethanol–water as needles, m. p. 280° (decomp.) (Found: C, 65·2; H, 4·9; N, 13·6. $C_{11}H_{10}O_2N_2$ requires C, 65·4; H, 5·0; N, 13·85%). The pyrazolone gave a red colour with ferric chloride in aqueous alcohol.

Reaction of 4-1'-*Anilinoethylidene*-3-*phenyl*isoo*xazolid*-5-*one with Amidines.*—A solution of the *iso*oxazolidone (0·28 g.) and *p*-methanesulphonylbenzamidine (0·2 g.) in ethanol (5 ml.) was boiled under reflux for 15 min., ammonium carbonate subliming into the condenser; the clear solution with an equal volume of water gave 1-*amino*-1-*phenyl*-3-*phenyliminobut*-1-*ene* (0·1 g.) which separated from ethanol–water as pale yellow needles, m. p. 83° (Found: C, 81·35; H, 6·8; N, 11·95. $C_{16}H_{16}N_2$ requires C, 81·35; H, 6·8; N, 11·85%). A solution of the base (0·1 g.) in ether (5 ml.) with concentrated hydrochloric acid (1 drop) gave the *hydrochloride* (0·1 g.) as pale yellow needles (from ethanol–ether), m. p. 220° (decomp.) (Found: N, 10·1. $C_{16}H_{16}N_2$,HCl requires N, 10·3%). The base when boiled for a few minutes with dilute hydrochloric acid gave benzoylacetone. The same base was also obtained by reaction of the *iso*oxazolidone with acetamidine, benzamidine, guanidine, or sodium hydroxide.

Hydrogenation of 4-1'-*Anilinobenzylidene*-3-*phenyl*isoo*xazol*-5-*one.*—A suspension of the *iso*oxazolone (1 g.) in ethanol (50 ml.) was hydrogenated over platinum until 1 mol. of hydrogen

had been absorbed (3 hr.); a clear solution was obtained; evaporation *in vacuo* gave a crystalline residue; 1-*amino*-1 : 3-*diphenyl*-3-*phenyliminopropene* (0·8 g.) separated from ether–light petroleum as yellow needles, m. p. 127° (Found : C, 84·85; H, 6·05; N, 9·1. $C_{21}H_{18}N_2$ requires C, 84·55; H, 6·1; N, 9·4%). The base (0·1 g.) gave, as above, the *hydrochloride* (0·1 g.), pale yellow needles (from ethanol–ether), m. p. 215° (decomp.) (Found : N, 8·45. $C_{21}H_{18}N_2$,HCl requires N, 8·35%). The base (0·1 g.) was boiled with N-hydrochloric acid (3 ml.) for a few min.; a clear solution was obtained which rapidly became turbid and when cooled gave dibenzoylmethane (0·05 g.) as colourless prisms (from ethanol–water), m. p. 77° not depressed when admixed with an authentic specimen of m. p. 76—77°.

5-*Methoxy*-3-*methyl*-4-p-*toluidinomethylene*iso*oxazoline* (IX).—A suspension of finely ground 3-methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one (1 g.) in ether (50 ml.) containing methanol (1 ml.) was set aside with an excess of ethereal diazomethane at room temperature with occasional shaking until a clear solution was obtained (2 days). Evaporation then gave a solid residue; 5-*methoxy*-3-*methyl*-4-p-*toluidinomethylene*iso*oxazoline* (0·75 g.) separated from ethanol–water as pale yellow needles, m. p. 138° (Found : C, 66·8; H, 6·7; N, 12·0. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·95; N, 12·05%). This (0·1 g.) gave, as above, the *hydrochloride* (0·1 g.), yellow needles (from ethanol–ether), m. p. 184° (decomp.) (Found : C, 58·15; H, 6·35; N, 10·5. $C_{13}H_{16}O_2N_2$,HCl requires C, 58·1; H, 6·4; N, 10·4%). The *iso*oxazoline (0·5 g.) was boiled under reflux with 2N-hydrochloric acid (20 ml.) for 1 hour and the solution distilled until the volume was about 10 ml. The distillate contained acetone and gave the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 122°, thereof (Found : C, 45·55; H, 4·1. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·25%). The hydrolysis solution was basified with sodium hydroxide solution, and air aspirated through it, the vapour being condensed in dilute hydrochloric acid; evaporation of the acid solution gave ammonium chloride (0·1 g.). The alkaline solution was extracted with ether (2 × 10 ml.) to give a base, the acetyl derivative of which had m. p. 145°, undepressed when mixed with aceto-*p*-toluidide, m. p. 146°. A solution of the *iso*oxazoline (1 g.) in methyl acetate (20 ml.) was hydrogenated over platinum until 1 mol. of hydrogen had been absorbed (2 hr.); evaporation *in vacuo* and addition of ether gave a *substance* (0·25 g.), which separated from ethanol as pale yellow needles, m. p. 210° (Found : C, 58·3; H, 6·55; N, 6·0. $C_{11}H_{15}O_4N$ requires C, 58·65; H, 6·7; N, 6·2%).

The authors thank Dr. E. Challen for the semimicro-analyses.

THE UNIVERSITY OF TECHNOLOGY,
SYDNEY, N.S.W., AUSTRALIA.

[*Received, June 24th,* 1953.]

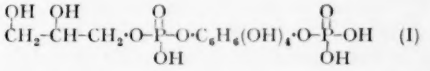
698. *The Structure of the Glycerinositophosphatide of Ground-nut.*

By T. MALKIN and A. G. POOLE.

By means of paper-chromatographic checks during fractionation, the inositol-containing phosphatide of ground-nuts, which comprises some 38% of the phosphatides present, has been isolated in a high degree of purity. It differs from other known phosphatides in having a nitrogen–phosphorus ratio of 1 : 2, and its degradation products are not inconsistent with structure (II), namely, the *N*-glycosyl derivative of the ethanolamine ester of phosphatidylinositol phosphate. Each molecule of phosphatide contains two molecules of L-arabinose and one of D-galactose. Mild hydrolysis gives a disaccharide of arabinose and galactose, but the detailed arrangement of the three sugar molecules is not yet known.

THE presence of inositol in phospholipids was first noted by Anderson (*J. Amer. Chem. Soc.*, 1930, **52**, 1607) in tubercle lipids (cf. Anderson and Roberts, *ibid.*, p. 5023; Cason and Anderson, *J. Biol. Chem.*, 1938, **126**, 527; de Sütö-Nagy, and Anderson, *ibid.*, 1947, **171**, 761). It has also been found in soya-bean lecithin by Klenk and Sakai (*Z. physiol. Chem.*, 1939, **258**, 33) and by Woolley (*J. Biol. Chem.*, 1943, **147**, 581), in ox-brain kephalin by Folch and Woolley (*ibid.*, 1942, **142**, 963; cf. Folch, *ibid.*, 1949, **177**, 505), and in ground-nut kephalin by Hutt, Malkin, Poole, and Watt (*Nature*, 1950, **165**, 314).

Little is known concerning the structure of inositol phospholipids, and the evidence is too slender even to decide whether the various workers were dealing with the same compounds; but there are common features in the papers mentioned which suggest the existence of a phosphatide, or a closely related group of phosphatides, based on the glycerol ester (I) of inositol diphosphate.



(I)

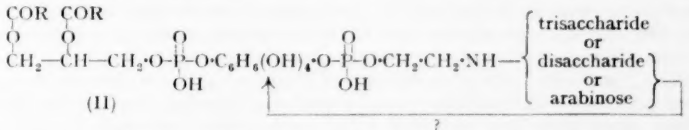
Thus, on hydrolysis of the various phosphatides, Klenk and Sakai found inositol and glycerol monophosphates; de Sütö-Nagy, and Anderson found an acid $C_9H_{20}O_{14}P_2$, which on further hydrolysis gave equimolecular amounts of the same two monophosphates; Folch found equimolecular amounts of inositol "*meta*"-diphosphate and glycerol, and Woolley found inositol phosphate.

Continuing our earlier work (Hutt *et al.*, *loc. cit.*) we have now obtained a more homogeneous fraction by carrying out chromatographic checks during the fractional precipitations of the mixed phosphatides, in order to ensure that only one nitrogenous base was present. In this way, we have obtained a product, some 38% of the ground-nut phosphatide, which contains ethanolamine as the only base. It is a colourless powder, which darkens slightly on storage and responds to the Scherer test for inositol, the acraldehyde test for glycerol, and the Molisch test for carbohydrates; but it does not reduce Fehling's solution until after hydrolysis with dilute mineral acid, *i.e.*, the sugars are combined through glycosidic groups. The nitrogen–phosphorus ratio is 1 : 2, in contrast to that of other known phosphatides—lecithin and kephalin 1 : 1, sphingomyelin 2 : 1.

Analysis of the acid hydrolysis products of this glycerinositophosphatide by paper partition chromatography showed the presence of α- and β-glycerophosphoric acid, inositophosphoric acid, ethanolamine, ethanolamine phosphate, arabinose, and a disaccharide which could be further hydrolysed to arabinose and galactose. The glycerol and inositol phosphates were isolated and found to be in the molecular ratio 1 : 1, and the parent inositol was found to be the inactive form, m. p. 222°. Estimated by Hirst and Jones's method (*J.*, 1948, 1679; 1949, 1659), the molecular ratio of arabinose to galactose was 2 : 1. The two sugars were identified as L-arabinose and D-galactose.

Alkaline hydrolysis of the phospholipid yielded some 40% (by weight) of fatty acids. These were not examined exhaustively, but in agreement with Hilditch and Zaky's report (*Biochem. J.*, 1942, **36**, 815) they were found to be mainly saturated and unsaturated C_{16} and C_{18} acids.

These results would agree with a structure (II) for the glycerinositophosphatide, but we found nitrogen and phosphorus values too high, and the acetyl value too low, indicating a lower sugar content. It is possible that the sugar-free phosphatide occurs naturally, as such, or that the sugar may have been lost by enzyme action in the ground-nut or during extraction of the phosphatide.



(II)

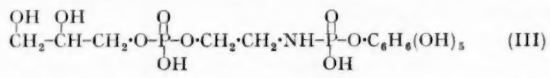
R·CO = mainly palmitoyl, stearoyl, oleoyl, linoleoyl.

In order to remove the analytical uncertainty due to the presence of an indefinite mixture of fatty acids, we removed the latter by alkaline alcoholysis, and after a purification by means of neutral and basic lead acetates we obtained a homogeneous product, which on chromatographic analysis in three solvent mixtures gave a single distinct spot when tested either for sugars or phosphates.

This product is a white crystalline solid, which is very hygroscopic and extremely insoluble in alcohol. It responds to the Molisch, Scherer, and acraldehyde tests, but does not give Fehling's or the ninhydrin test until after hydrolysis with dilute mineral acid.

Its analyses are correct for (II), with the fatty acid radicals removed, and its equivalent weight is 444 (alkali titration; theor. mol. wt., 883). Titration to light-screened methyl red showed that the phosphate groups are in the same state of acidity. Examination of the acid hydrolysis products showed that glycerol and inositol monophosphates were present in the ratio 1 : 1, and arabinose and galactose in the ratio 2 : 1.

As one of us (A. G. P.) has had to discontinue this work, it is reported with a few points still undecided. Thus, although Folch isolated inositol "*meta*"-diphosphate, the positions of the phosphate groups in the original phosphatide are uncertain, owing to the possibility of migration of the phosphate groups during hydrolysis. Again, the negative ninhydrin test before hydrolysis suggests presence of a *N*-glycosyl derivative; but it has still to be determined whether the sugars are present as a trisaccharide, or as a mono- and di-saccharide with one of the sugars combined with inositol. Other possible explanations



(III)

of the negative ninhydrin test are not excluded, *e.g.*, structure (III) with the sugars attached to inositol, although this could not give rise to inositol diphosphate. The above points are under investigation.

Experimental

Our raw material was commercial ground-nut "lecithin," kindly provided by Messrs. J. Bibby & Sons, Ltd. It is a dark viscous oil, which for technical purposes contains a quantity of refined vegetable oil. This was removed as follows: A solution of crude "lecithin" (100 g.) in ether (200 c.c.) was poured, with stirring, into ten times its volume of acetone. The precipitate was allowed to settle overnight, and the mother-liquor was decanted. The somewhat sticky residue was stirred with acetone (400 c.c.) until it became more granular, and was filtered off. Two repetitions of this process yielded 62 g. of a dark brown, friable but slightly sticky, solid.

Isolation of the "Kephalin" Fraction.—The above phospholipid mixture (100 g.), dissolved in ether (200 c.c.), was poured slowly into ethanol (1 l.) with vigorous stirring. After 12 hr., the precipitate was filtered off and washed with 5 : 1 ethanol–ether, followed by ethanol. The solvent was removed *in vacuo*, and the whole process was repeated twice. The product was a light brown friable powder (63·2 g.).

Determination of the Bases.—After first hydrolysing the phospholipid fraction as described below, we used the chromatographic method of Chargaff, Levene, and Green (*J. Biol. Chem.*, 1948, **175**, 67). 50 mg. of material were emulsified with 5 c.c. of 6N-hydrochloric acid, and refluxed for 12 hr. After cooling overnight in the refrigerator, the solid cake of fatty acids which separated was filtered off, and the filtrate was evaporated to dryness *in vacuo* over potassium hydroxide. The residue was dissolved in a few drops of water, and the resulting syrup was used for the chromatographic analysis.

The hydrolysate of the above "kephalin" fraction contained ethanolamine phosphate, choline chloride, ethanolamine hydrochloride, and serine (R_F 0·02, 0·11, 0·32, and 0·55 respectively). This so-called "kephalin" is therefore a complex mixture.

Isolation of Glycerinositophosphatide (X).—We adopted the method used by Folch (*J. Biol. Chem.*, 1942, **146**, 35) who has shown that fractional precipitation from chloroform solution by ethanol is an effective method for separating phospholipid mixtures.

To the above "kephalin" (20 g.) in chloroform (160 c.c.), ethanol (180 c.c.) was added with vigorous stirring. The initial turbidity cleared gradually, leaving a viscous lower layer, from which the clear upper layer was decanted. The viscous layer was then stirred with ethanol (50 c.c.), and the solid which separated was filtered off, washed with ethanol, and dried *in vacuo* (P_2O_5), giving fraction I (14·7 g.).

Ethanol (55 c.c.) was added with stirring to the supernatant liquid from fraction I. A viscous layer separated overnight, and was treated as above, giving fraction II (1·8 g.).

The mother-liquor from fraction II was poured, with stirring, into ethanol (500 c.c.) and the solid which separated overnight was filtered off, washed with ethanol, and dried *in vacuo*, giving fraction III (1 g.).

On concentration of the mother-liquor from fraction III to half its volume and cooling in the refrigerator overnight, a small amount of solid separated. After filtration, washing with ethanol, and drying, fraction IV remained as a slightly sticky powder (0·23 g.).

The filtrate from fraction IV was concentrated to 20 c.c. and poured into acetone (100 c.c.). A yellowish pasty material, which could not be filtered, was precipitated. After decantation of the mother-liquor, trituration with one or two changes of acetone, and removal of solvent there remained fraction V (0·15 g.).

The various fractions were submitted to Molisch, Scherer, and chromatographic tests with the results recorded in the Table. These show that fraction I contains the bulk of the glycerinositophosphatide together with a little phosphatidylserine. The latter is concentrated in fraction III, whilst fractions IV and V contain mainly phosphatidyl-choline and -ethanolamine (the classical lecithin and kephalin).

Fraction	Molisch	Scherer	Bases present	Concn.
I	Strong	Strong	Serine	Weak
			Ethanolamine HCl	Strong
			,, phosphate	,,
II	,,	,,	Serine	,,
			Ethanolamine HCl	Weak
			,, phosphate	,,
III	Weak	Weak	Serine	Strong
			Ethanolamine HCl	Weak
			,, phosphate	V. weak
IV	Negative	Negative	Serine	Weak
			Choline chloride	Strong
			Ethanolamine HCl	,,
V	,,	,,	Choline chloride	,,
			Ethanolamine HCl	,,

Further purification of fraction I. Fraction I (20 g.), dissolved in chloroform (200 c.c.), was poured with vigorous stirring into ethanol (250 c.c.). The viscous layer which gradually separated was triturated with ethanol, to bring about solidification, and filtered off. This process was carried out five times and the solid residue was then dried *in vacuo* (yield, 17·3 g.). In order to remove possible inorganic impurities, this product was submitted to dialysis as follows. The phospholipid (10 g.) was emulsified with water (100 c.c.) and placed in a Cellophane container surrounded by distilled water. The latter was changed every 12 hr. for 2 days. The emulsion was then concentrated to 10 c.c. under reduced pressure at 40°; frothing prevented further concentration. Final drying was carried out at −50°/0·1 mm., to yield a fine white powder which, after trituration with acetone (20 c.c.), was filtered off at the pump and dried *in vacuo*, giving 9·3 g., m. p. 209—210° (decomp.). The only nitrogenous bases present in the hydrolysate of this material were ethanolamine and ethanolamine phosphate. The final yield of glycerinositophosphatide (X) is *ca.* 60% of the crude kephalin (38% of the total ground-nut phosphatide).

General Properties of the Above Glycerinositophosphatide (X).—The material (X) is a pale brown, friable solid, soluble in chloroform, benzene, and to some extent in ether (not if sodium-dried). The solubility in all these solvents is increased by the addition of a few drops of water. It is insoluble in acetone, ethanol, and cold glacial acetic acid, but dissolves in hot acetic acid. It gives the Molisch, Scherer, and acraldehyde test, but does not reduce Fehling's solution until after hydrolysis with dilute mineral acid. When ignited, it gives an inorganic residue containing sodium, potassium, and phosphate. Lead acetate and barium chloride solutions precipitate the phospholipid from its aqueous emulsion.

Analytical values were: C, 53·0; H, 8·5; N, 1·26; P, 5·2; Ac, 11·4%. Equimolecular proportions of palmitic and oleic acids (the known major constituent acids) being assumed, formula (II), $C_{61}H_{113}O_{29}NP_2$, requires C, 52·8; H, 8·2; N, 1·01; P, 4·6; Ac, 14·7%. High accuracy cannot be expected in view of the above assumption, and also because of the small unknown content of sodium and potassium. The most significant feature is the N–P ratio of 1 : 1·85, in marked contrast to those (1 : 1 and 2 : 1) hitherto found for phosphatides. The acetyl value indicates that there has been some loss of sugar, possibly in the technical extraction of the phosphatide.

Bases Present.—The only basic substances found were ethanolamine (R_F 0·53) and ethanolamine phosphate (R_F 0·2). At the time, the latter had not been identified among the hydrolysis products of phospholipids and a few mg. were extracted with boiling water from the appropriate section of the chromatogram paper and compared with synthetic ethanolamine phosphate (obtained in 48% yield by Outhouse's method, *Biochem. J.*, 1936, **30**, 197). Chromatographic

comparison with ninhydrin and phosphate sprays showed identity, and the m. p.s of the flavianates of synthetic, natural, and mixed products were 225°, 224°, and 224°, respectively.

Identification of Other Hydrolysis Products.—(*a*) *Glycerol and inositol phosphates.* For paper partition (Hanes and Isherwood, *Nature*, 1949, **164**, 1107), basic acetate–pyridine–water was the most suitable mixture [water-poor phase from ethyl acetate (100 c.c.), pyridine (45 c.c.), and water (100 c.c.)]. The glycerinositophosphatide (0·800 g.) was emulsified with N-sulphuric acid (50 c.c.) and heated for 6 hr. on a boiling-water bath. The insoluble precipitate of fatty acids, which formed overnight, was filtered off and the filtrate was neutralised with barium hydroxide solution (phenolphthalein). Insoluble barium salts were filtered off and the filtrate was treated with sufficient ammonium sulphate to precipitate the remaining barium. After filtration, water was distilled off *in vacuo* and the resulting syrupy liquid which contained ammonium salts of phosphoric esters, was chromatographed (see above) for 36 hr. at 18°. The dried paper was sprayed with the perchloric acid–ammonium molybdate spray (Hanes *et al.*). In addition to an indistinct spot near the starting point, probably due to traces of the slow-moving ethanolamine phosphate, there appeared three more distinct spots of R_P 0·25, 0·68, and 0·75, which were in agreement with values found for authentic ammonium salts of inositol phosphate (or mixture of phosphates) and α- and β-glycerophosphate, respectively.

More drastic hydrolysis yielded glycerol and inositol: The glycerinositophosphatide (100 mg.) was heated in a sealed tube with 3N-sulphuric acid (2 c.c.) for 4 hr. at 160—170°. On cooling, the precipitated fatty acids were filtered off and the filtrate was neutralised with barium carbonate. After filtration from the barium salts, the filtrate was concentrated *in vacuo* to a syrup. This was spotted, together with glycerol and inositol, on a paper chromatogram which was run for 12 hr. (butanol–water), and then sprayed with ammoniacal silver nitrate. The syrup yielded two spots of R_P 0·03 and 0·33, which agreed with those of inositol and glycerol, respectively.

Isolation of phosphoric esters. The glycerinositophosphatide (10 g.) was refluxed for 6 hr. with concentrated sulphuric acid (2·5 g.) in methanol (100 c.c.). After cooling, the methanol was removed *in vacuo* and the residue was extracted with water (50 c.c.). Insoluble material was filtered off and the filtrate was extracted with light petroleum (b. p. 40—60°) to remove traces of fatty material, concentrated *in vacuo* to *ca.* 20 c.c., and neutralised with barium hydroxide solution (thymolphthalein). Insoluble barium salts were filtered off, and the filtrate was concentrated by distillation under reduced pressure in a carbon dioxide-free atmosphere. Trituration of the syrupy residue with ethanol precipitated the barium salts of the phosphate esters, which were filtered off, washed with ethanol, and dried (yield, 5 g.). Should the product at this stage give a slight Molisch test, traces of carbohydrates are removed by Soxhlet extraction with 90% ethanol.

The barium salts were dissolved in distilled water (20 c.c.), and the barium was removed by exact neutralisation with dilute sulphuric acid and filtration. The filtrate was concentrated to dryness *in vacuo* and the resulting syrup triturated with ethanol (10 c.c.) which caused precipitation of a solid (A) which was filtered off (see below).

Isolation of barium glycerophosphate. The above filtrate was concentrated *in vacuo*; a small amount of solid which separated was filtered off. After complete removal of the ethanol, the resulting syrup was dissolved in water (2 c.c.) and neutralised with a saturated solution of barium hydroxide (thymolphthalein) and poured into twice its volume of ethanol. After being kept overnight in the refrigerator the crystalline precipitate which had separated was filtered off, washed with ethanol, and dried (P_2O_5) *in vacuo* (yield, 1·9 g.) (Found: C, 12·0; H, 2·1; P, 9·6. Calc. for $C_3H_7O_6PBa$: C, 11·7; H, 2·3; P, 10·1%).

This barium salt (1 g.) was hydrolysed with 3N-sulphuric acid (5 c.c.) at 160—170° in a sealed tube for 3 hr. After removal of the sulphuric acid (barium carbonate) and concentration *in vacuo*, the resulting syrup gave a single spot corresponding to glycerol when submitted to chromatographic analysis. The remainder of the syrup (0·25 g.), when benzoylated in pyridine, gave a 90% yield of glycerol tribenzoate, m. p. and mixed m. p. 76° (from light petroleum).

Inositol dihydrogen monophosphate. Solid A (above), when dried *in vacuo* (P_2O_5), was a white crystalline, slightly hygroscopic solid (1·8 g.), acid to litmus and Congo-red, and responding to the Scherer test (Found, in a sample dried over P_2O_5 at 118° *in vacuo*: C, 27·3; H, 5·1; P, 11·55. Calc. for $C_6H_{13}O_9P$: C, 27·7; H, 5·0; P, 11·9%). Two equivalent weights were found, *viz.*, 257·8 (screened methyl-red) and 128·3 (thymolphthalein) (calc.: 260, 130).

Barium inositol monophosphate. The above acid (1 g.), dissolved in water (1 c.c.), was neutralised (thymolphthalein) with saturated barium hydroxide solution. A faint precipitate was removed by filtration and the filtrate was concentrated to *ca.* 5 c.c. and poured into ethanol

(10 c.c.). The resulting precipitate (1·5 g.) was filtered off, washed with ethanol and dried over P_2O_5 *in vacuo* at 118° (Found: C, 18·1; H, 3·0; P, 7·85. Calc. for $C_6H_{11}O_9PBa$: C, 18·2; H, 2·8; P, 7·8%). This barium salt (20 mg.) was converted into the ammonium salt for chromatographic analysis as described earlier, and analysed for phosphate (ethyl acetate–pyridine–water). One spot only was observed, of R_P 0·24, compared with 0·25 found for the ammonium salt of one of the phosphate esters produced on hydrolysis.

Isolation of inositol. The above barium salt (1·4 g.) was hydrolysed by heating with 3N-sulphuric acid (5 c.c.) at 160—170° in a sealed tube for 3 hr. After cooling, the mixture was neutralised with barium carbonate and the insoluble barium salts were filtered off. The filtrate was taken to dryness *in vacuo*, and the solid residue was triturated with ethanol. After filtration, washing with ethanol, and drying, there remained 0·53 g. of crystalline material. Crystallisation from water yielded 0·47 g. of optically inactive crystalline material, m. p. 220°; the mixed m. p. with inactive inositol was 222°. The identity was also confirmed through the hexa-acetate, m. p. 218°.

Identification and isolation of sugars. The glycerinositophosphatide (50 mg.) was hydrolysed with 0·5N-sulphuric acid (2 c.c.) in a sealed tube at 100° for 12 hr. After cooling, fatty acids were removed by filtration, and the filtrate was neutralised with barium carbonate, filtered, and concentrated to a thin syrup by distillation under reduced pressure. Spots of this syrup and a standard mixture containing galactose, arabinose, ribose, and rhamnose were placed on a paper chromatogram, which was run for 24 hr. (*n*-butanol saturated with water as mobile phase). The paper was dried, sprayed with ammoniacal silver nitrate, and heated in front of an electric fire. Two spots appeared corresponding closely in R_F to galactose and arabinose, but as mannose and fructose have R_G close to that of arabinose, the presence of the latter was confirmed by a similar analysis of a mixture containing galactose, arabinose, fructose, and mannose (spraying with a 1 : 1 mixture of 5% aqueous trichloroacetic acid and 1% alcoholic aniline, which gives a rose-red spot with pentoses, and brown spot with hexoses; cf. Hough, Jones, and Wadman, *J.*, 1950, 1702).

Weaker acid hydrolysis. In order to determine the nature of the original saccharide present, the glycerinositophosphatide (50 mg.) was refluxed for 12 hr. with 0·01N-sulphuric acid (5 c.c.). The mixture was cooled and filtered through a "Filtercel" pad. After neutralisation with barium carbonate, and removal of barium salts by filtration, the filtrate was evaporated *in vacuo* to a thin syrup and submitted to chromatographic analysis, as above. Silver nitrate showed the presence of a new slower-moving sugar and arabinose, and the aniline–trichloroacetic acid mixture gave a brown spot for the slow-moving sugar and confirmed the presence of arabinose by a rose-pink spot.

On further hydrolysis of the syrup with 0·5N-sulphuric acid in a sealed tube at 100° for 12 hr., neutralisation, concentration, and chromatographic analysis, as above, gave a syrup, containing galactose and arabinose, the latter being present in larger amount than in the previous experiment. It appeared therefore that the slow-moving sugar was probably a disaccharide containing galactose and arabinose. In order to confirm this, a broad chromatogram was started with a large number of drops of the syrup. The position of the slow-moving sugar was found by developing a thin strip, and the remainder of the chromatogram containing this spot was cut out and extracted with water. The extract was evaporated to a syrup and hydrolysed by 0·5N-sulphuric acid (1 c.c.) in a sealed tube for 12 hr. at 100°; after neutralisation and concentration as above described, chromatographic analysis showed the presence of both galactose and arabinose.

Molecular ratio of sugars present. The method used for the quantitative estimation of the sugars was that described by Hirst and Jones (*J.*, 1949, 1659) (cf. also Flood, Hirst, and Jones, *J.*, 1948, 1679), based on paper-chromatographic separation of the sugars and subsequent determination by titration of the formic acid liberated on oxidation with sodium periodate. The glycerinositophosphatide (100 mg.) was hydrolysed with 0·5N-sulphuric acid, as described above under the identification of sugars, and the sugars were obtained as a thin syrup. Uniform drops of the latter were placed at intervals of 0·5 cm. on the starting line of a Whatman No. 1 filter-paper sheet, by means of a hypodermic syringe fitted with a micrometer screwhead. In order to obtain uniform bands on the chromatogram, it is important that the drops should be of the same volume, and that they should not be allowed to coalesce. The chromatogram was then run for 54 hr. (butanol–water) in a covered tank well protected from draught. After drying, thin strips were cut from both edges and from the centre of the filter paper sheet, and developed in order to locate the positions of the sugar zones. These were then cut out from the undeveloped chromatogram, and extracted with hot water, by suspension from the bottom

of a coil reflux condenser (see Flood *et al.*, *loc. cit.*, p. 1681, for details). To each extract (*ca.* 5 c.c.) 0·25M-sodium periodate (0·5 c.c.) was added, and the solution was heated under a reflux for 20 min. After cooling, excess of periodate was destroyed by ethylene glycol (0·5 c.c.), and the solution was titrated against 0·01N-sodium hydroxide (light-screened methyl-red). Blanks were carried out simultaneously on portions of the chromatogram which contained no sugar. The following values were obtained: galactose required 0·94 c.c. of 0·01N-NaOH, equiv. to 0·338 mg. of galactose; * arabinose required 1·74 c.c. of 0·01N-NaOH, equiv. to 0·653 mg. of arabinose.* Mol. ratio, galactose : arabinose = 1 : 2·3.

Isolation and characterisation of L-*arabinose and* D-*galactose.* The sugars obtained by acid hydrolysis were separated on a column of powdered cellulose (*n*-butanol–water), with the automatic receiver changer described by Hough, Jones, and Wadman, *J.*, 1949, 2511.

Acid Hydrolysis of the Glycerinositophosphatide (*X*).—The phosphatide (5 g.) was refluxed for 8 hr. with 4% methanolic hydrogen chloride (20 c.c.). After cooling and filtration, the solvent was removed from the filtrate *in vacuo*, leaving a viscous syrup. This was dissolved in water (1 c.c.) and neutralised by passage down a small glass column packed with Amberlite IR-4B. The resulting solution of methyl glycosides was concentrated *in vacuo* to a syrup. This was hydrolysed with N-sulphuric acid (2 c.c.) in a sealed tube at 100° for 2 hr. The hydrolysate was neutralised ($BaCO_3$), filtered, and concentrated to dryness by distillation of solvent *in vacuo*. A paper chromatogram of the resulting syrup showed the presence of galactose and arabinose. The remainder of the syrup, dissolved in *n*-butanol (1 c.c.), was placed on top of a cellulose column and washed on to the column with several 1-c.c. portions of *n*-butanol–water. The constant-head reservoir which contained this solvent mixture was then placed in position and run for 3 days, after which it was placed over the constant receiver-changer. Two chromatographically pure fractions were obtained, and these were evaporated to dryness *in vacuo* and extracted with ether in order to remove traces of oily impurity. Each fraction was dissolved in water (2 c.c.), filtered through a sintered-glass funnel, and concentrated *in vacuo* (over P_2O_5), whereupon the sugars crystallised. They were triturated with ethanol, filtered, and dried, yielding fractions 1 (31·1 mg.) and 2 (15·3 mg.).

Fraction 1. $[\alpha]_D^{20}$ +108° (equilibrium) and R_G 0·12 agree with those of authentic L-arabinose. 20 mg. yielded 32 mg. of toluene-*p*-sulphonylhydrazone, m. p. and mixed m. p. 154°. 10 mg. yielded 19·6 mg. of arabinosazone, m. p. and mixed m. p. 165°.

Fraction 2. $[\alpha]_D^{20}$ +82·9° (equilibrium) and R_G 0·07 agreed with those of D-galactose. 8 mg. yielded 13·8 mg. of an osazone with the characteristic appearance of galactosazone under the microscope, and m. p. 196° (mixed m. p. 195°). 6 mg., oxidised with nitric acid, yielded 6 mg. of an acid, m. p. 211°; the mixed m. p. with mucic acid (213°) was 212°.

Alkaline Hydrolysis of Glycerinositophosphatide (*X*).—The phosphatide (40 g.) was dissolved in moist benzene (400 c.c.) and to the cold solution was added a solution of potassium hydroxide (9·6 g.) in methanol (120 c.c.). A gelatinous precipitate separated after about 10 min. After 20 hr., with occasional shaking, at room temperature, the precipitate was filtered off at the pump and washed with several changes of 3 : 1 benzene–methanol. The filtrate and washings, which contained soaps and fatty methyl esters, were retained.

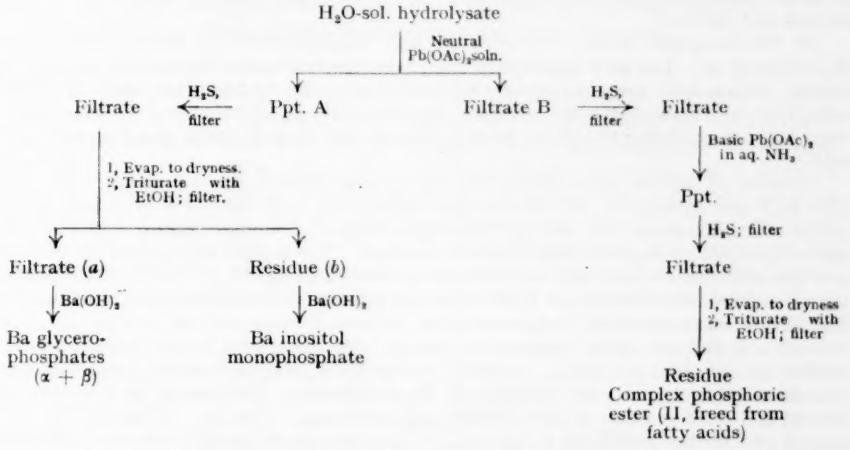
The precipitate was extracted with water (200 c.c.), and the cloudy solution acidified with acetic acid and extracted with light petroleum (b. p. 40—60°). The aqueous layer was clarified by filtration through a No. 3 sintered-glass funnel with the aid of a "Filtercel" pad. Excess of acetic acid was removed from the filtrate by several extractions with ether, and the solution was concentrated to about 80 c.c. The phosphoric esters present were separated according to the scheme on page 3477.

Neutral lead acetate precipitation. A slight excess of a saturated solution of neutral lead acetate was added to the above aqueous hydrolysate and the mixture was shaken vigorously from time to time and kept overnight. The lead salts (precipitate A in scheme) were then filtered off ("Filtercel" pad), washed well with distilled water, suspended in distilled water (20 c.c.) and treated as shown in the scheme. The filtrate (*a*) and washings were concentrated to dryness *in vacuo* and the residue was dissolved in water (2 c.c.). The strongly acid solution was neutralised with aqueous barium hydroxide and poured into twice its volume of ethanol. The resulting precipitate was filtered off and dried *in vacuo* (P_2O_5) (yield, 90·6 mg.). By the methods already described it was shown to be a mixture of barium salts of α- and β-glycero-

* Calc. on the basis of 100% conversion into formic acid: conversion is nearer 95 ± 3%, but this does not greatly affect the mol. ratio of the sugars. The ratio found supports the view expressed earlier that some of the phosphatide has lost part of the sugar fragment, probably in the form of a galactose–arabinose disaccharide.

phosphates. The residue (*b*), similarly treated, gave a precipitate (98·3 mg.) of the barium salt of inositol phosphate.

The filtrate B and washings were freed from lead and concentrated *in vacuo* to 20 c.c. This solution was neutral to Congo-red, but acid to litmus, and gave a strong positive test for phosphate, and hence, presumably, contained a phosphate ester. This was precipitated by the



addition of slight excess of a saturated solution of basic lead acetate in 4% aqueous ammonia. The white lead salt was filtered through a No. 3 sintered glass funnel, well washed with distilled water, suspended in distilled water (300 c.c.), and treated as shown in the scheme. The final crystalline residue (dried *in vacuo* at room temperature over P_2O_5) was triturated with ethanol, filtered off at the pump, and well washed with ethanol. It was dried at room temperature in a high vacuum (P_2O_5) (yield, 3·1 g.).

The resulting complex *ester* (Y) is a white, crystalline, extremely hygroscopic solid (Found : C, 36·5; H, 5·8; N, 1·46; P, 6·8. $C_{27}H_{51}O_{27}NP_2$ requires C, 36·7; H, 5·8; N, 1·58; P, 7·0%). It contains nitrogen and phosphorus, and gives positive tests for carbohydrates (Molisch), inositol (Scherer), and glycerol. It does not reduce Fehling's solution or give the ninhydrin test until after hydrolysis with dilute mineral acid.

Approx. 150 mg. of the phosphate were dried at 61° (P_2O_5) in a high vacuum, weighed, and dissolved in distilled water (to give 50 c.c.). Portions (10 c.c.) were titrated against 0·01N-sodium hydroxide (phenolphthalein) [Found : Equiv., 445·4. (II) requires Equiv., 441·5]. When light-screened methyl-red was used as indicator, only one drop of the standard alkali was required for neutralisation *i.e.*, there is no strong acid equivalent, and both phosphate groups are in the same state of weak acidity.

Chromatograms of the Complex Phosphate (*Y*).—This ester was subjected to paper chromatography, with the following solvent mixtures and spraying with both sugar and phosphate spray reagents : (1) *n*-butanol saturated with water; (2) *n*-butanol saturated with water–morpholine (3 : 1); (3) pyridine–ethyl acetate–water [water-poor phase from pyridine (45 c.c.), ethyl acetate (100 c.c.), and water (100 c.c.)]. Each paper was run for 60 hr., and one half was sprayed with ammoniacal silver nitrate and the other with perchloric acid–molybdate reagent. All the papers showed one distinct spot only, independent of which spray was used, and it was concluded that the compound is a single homogeneous substance.

Acid Hydrolysis of the Glycerinositophosphate (*Y*).—(1) *To galactose and arabinose.* The ester (20 mg.) was hydrolysed in a sealed tube at 100° for 12 hr. with 0·5N-sulphuric acid (1 c.c.). After being freed from sulphuric acid ($BaCO_3$) the neutral filtrate was concentrated *in vacuo* to a syrup which on chromatographic analysis as described earlier gave two spots corresponding in R_G and colour to galactose and arabinose.

(2) *Bases.* The ester (30 mg.) was hydrolysed by refluxing with 6N-hydrochloric acid (3 c.c.) for 12 hr. After evaporation to dryness *in vacuo* (over KOH), the residue was dissolved in water (1 c.c.), neutralised with sodium hydroxide solution, and submitted to paper chromatographic analysis together with a mixture containing 2-aminoethyl phosphate and ethanolamine

hydrochloride. A 3 : 1 mixture of *n*-butanol saturated with water and morpholine was used as the mobile phase. The paper was sprayed with ninhydrin and showed the presence of ethanolamine and 2-aminoethyl phosphate.

(3) *To inositol and glycerol.* The ester (20 mg.) was hydrolysed with 3N-sulphuric acid (1 c.c.) at 160° in a sealed tube for 3 hr. After neutralisation ($BaCO_3$), filtration, and concentration *in vacuo*, paper-partition chromatography (*n*-butanol–water) showed the presence of inactive inositol and glycerol.

(4) *The phosphoric acids.* The ester (10 mg.) was hydrolysed by boiling 2N-sulphuric acid (2 c.c.) for 6 hr. The hydrolysate was freed from sulphuric acid (barium hydroxide), and the soluble barium salts were converted into ammonium salts as described earlier (p. 3474), and submitted to chromatographic analysis (ethyl acetate–pyridine–water). Three spots were observed, corresponding to salts of inositol monophosphoric acid and α- and β-glycerophosphoric acid.

Isolation of barium glycerophosphate and barium inositol monophosphate. The ester (Y) (150 mg.) was hydrolysed with 2N-sulphuric acid (5 c.c.) at 100° for 6 hr. The solution was cooled and neutralised with barium hydroxide solution (thymolphthalein), and after filtration was evaporated to dryness under reduced pressure. The residue was triturated with ethanol, and the insoluble barium salts were filtered off and dried (yield, 112 mg.). The barium salts were dissolved in a few c.c. of water, and the barium was quantitatively removed (H_2SO_4). The filtrate was evaporated to dryness under reduced pressure and the residue triturated with ethanol and filtered. After removal of ethanol from the filtrate under reduced pressure, the residue was dissolved in a few c.c. of water, neutralised (barium hydroxide), poured into twice its volume of ethanol, and kept overnight in the refrigerator. The precipitated barium salt was filtered and dried *in vacuo* at 118° (P_2O_5) (yield, 45·3 mg.). The salt was shown, by chromatography and further hydrolysis to glycerol, to be a mixture of barium salts of α- and β-glycerophosphoric acid. The residue from the above trituration was dissolved in a few c.c. of water, neutralised (barium hydroxide), concentrated to a small volume, and poured into twice its volume of ethanol. The precipitated barium salt was filtered off and dried at 118° (P_2O_5) (yield, 60·9 mg.). This was shown by chromatography and further hydrolysis to inositol to be barium inositol monophosphate.

The molecular ratio of the glycerol and inositol phosphate found was 1 : 1·04.

Quantitative estimation of sugars. This was carried out by the periodate method described above. The glycerinositophosphate (60 mg.) was hydrolysed with 0·5N-sulphuric acid (2 c.c.) in a sealed tube at 100 for 12 hr. The galactose fraction required 0·81 c.c. of 0·01N-NaOH, equiv. to 0·2919 mg. of galactose, and the arabinose fraction required 1·23 c.c., equiv. to 0·4616 mg. of arabinose, being a molecular ratio, galactose–arabinose, 1 : 1·89.

Fatty Acid Content of Glycerinositophosphatide (*Y*).—Insofar as our results go beyond those of Hilditch and Zaky (*loc. cit.*), they are in agreement with theirs that the main acids present were oleic 47, linoleic 23, and palmitic 17%.

The retained filtrate and washings from the alkaline hydrolysis of the phosphatide were freed from solvent under reduced pressure and the residue was extracted with acetone and filtered. The filtrate contained methyl fatty esters (A), and the residue consisted of potassium soaps (B). Distillation of A yielded an oil (11·7 g.), b. p. *ca.* 147°/0·0084 mm. (I val., 86·9). Hydrogenation converted the oil into a white, crystalline solid (from methanol at −20°), m. p. 31—33°, which on saponification yielded an acid mixture, m. p. 67°, set point, 63°. The long *X*-ray spacing, m. p., and analysis agreed with those for a stearic-rich mixture of palmitic and stearic acids. The potassium salts, B, yielded acids (5·4 g.) (I val., 7·3). After hydrogenation and crystallisation from methanol, they had m. p. 66° and set point 62—64°, the *X*-ray spacing agreeing with that for a mixture of palmitic and stearic acids. The total amount of acid obtained was 16 g. (40% of the wt. of the phosphatide).

The above acids were obtained after somewhat mild hydrolysis at room temperature, but hydrolysis of a methanolic-benzene solution with boiling methanolic potassium hydroxide yielded much the same amount of fatty acid, which on no occasion exceeded 40·4%

We are grateful to Dr. J. K. N. Jones for his advice on sugar chromatography, and to Messrs. J. Bibby & Sons, Ltd., for supplies of ground-nut lecithin and for a grant. One of us (A. G. P.) expresses his thanks for the award of a Monsanto Fellowship.

THE UNIVERSITY, BRISTOL.

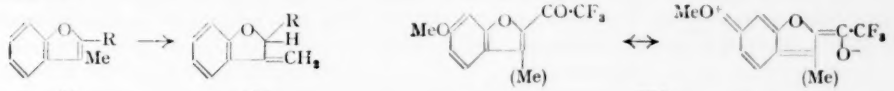
[*Received, June 8th,* 1953.]

699. *Organic Fluoro-compounds. Part VII.* Some 2-Trihalogenocoumarones.*

By W. B. Whalley.

This paper describes the application of the Hoesch reaction with trifluoromethyl and trichloromethyl cyanides to a series of coumarones.

Recent work in these laboratories (Dean, Halewood, Mongolsuk, Whalley, and Robertson, *J.*, 1953, 1250) has conclusively demonstrated that the isomerisation of usnic acid to usnolic acid involves, *inter al.*, the unexpected transformation of the angular methyl group of the coumarone system of usnic acid into the exocyclic methylene residue of usnolic acid. To obtain collateral information concerning this easy change we examined a series of coumarones of type (I) containing substituents in the α-position which might be expected to facilitate the conversion of (I) into the usnolic acid coumarone type (II). In view of our previous experience (cf. Whalley, *J.*, 1951, 3229), the trifluoroacetyl and trichloroacetyl residues seemed suitable for our purpose, and this communication describes the preparation and properties of a number of hydroxy- and methoxy-coumarones containing these moieties.



(I) (II) (III)

The application of the Hoesch ketone synthesis with trifluoro- and trichloro-methyl cyanides to 3-methylcoumarone, 6-hydroxy-, 6-methoxy-, 4 : 6-dimethoxy-, 5 : 6-dimethoxy-, 5-hydroxy-, and 5-methoxy-3-methylcoumarone gave the corresponding 2-trihalogenoacetyl derivatives (see table); 7-methoxy-3-methylcoumarone furnished a mixture

			Found, %.			Requires, %.		
2-Trifluoroacetylcoumarone	M. p.	Formula	C	H	F	C	H	F
3-Methyl-	54°	$C_{11}H_7O_2F_3$	—	—	24·4	—	—	25·0
6-Hydroxy-	168	$C_{10}H_5O_3F_3$	52·0	2·5	23·8	52·2	2·3	24·8
6-Hydroxy-3-methyl-	154	$C_{11}H_7O_3F_3$	54·7	3·3	—	54·1	2·9	—
4 : 6-Dimethoxy-3-methyl-	112	$C_{13}H_{11}O_4F_3$	53·8	3·5	18·9	54·2	3·8	19·4
5 : 6-Dimethoxy-	147	$C_{12}H_9O_4F_3$	52·7	3·4	21·1	52·6	3·3	20·8
5-Hydroxy-3-methyl-	171	$C_{11}H_7O_3F_3$	53·7	3·4	—	54·1	2·9	—
5-Methoxy-3-methyl-	97	$C_{12}H_9O_3F_3$	55·9	3·8	—	56·0	3·5	—
5-Methoxy-	85	$C_{11}H_7O_3F_3$	53·8	3·3	24·0	54·1	2·9	23·4

			Found, %.			Requires, %.		
2-Trichloroacetylcoumarone	M. p.	Formula	C	H	Cl	C	H	Cl
3-Methyl-	85°	$C_{11}H_7O_2Cl_3$	47·9	2·6	38·2	47·7	2·5	38·4
6-Hydroxy-	150	$C_{10}H_5O_3Cl_3$	43·0	2·1	37·2	43·0	1·8	37·9
6-Methoxy-	130	$C_{11}H_7O_3Cl_3$	45·0	2·6	36·2	45·1	2·4	36·3
4 : 6-Dimethoxy-3-methyl-	134	$C_{13}H_{11}O_4Cl_3$	46·2	3·2	31·4	46·3	3·3	31·6
5 : 6-Dimethoxy-3-methyl-	140	$C_{13}H_{11}O_4Cl_3$	46·6	3·4	31·1	46·3	3·3	31·6
5-Hydroxy-3-methyl-	168	$C_{11}H_7O_3Cl_3$	45·5	2·7	36·2	45·1	2·4	36·4
5-Methoxy-3-methyl-	108	$C_{12}H_9O_3Cl_3$	46·7	3·3	34·5	46·9	2·9	34·5

of 7-methoxy-3-methyl-2-trifluoroacetylcoumarone and an isomeric ketone which is probably either the 4- or 5-trifluoroacetyl compound. This is the first instance in which the application of the Hoesch ketone synthesis to a methoxy-3-methylcoumarone unsubstituted in the 2-position has furnished a derivative in which the entering substituent does not occupy that position.

5-Hydroxy-3-methylcoumarone failed to undergo the Gattermann aldehyde condensation or the Hoesch reaction with trifluoro- and trichloro-methyl cyanides, but the corresponding benzyl ether gave good yields of the respective ketones, debenzylation occurring during the Hoesch condensation. Modification of the usual reaction conditions (see Experimental) enabled the Hoesch reaction with these cyanides to be applied to a

* Part VI, *J.*, 1951, 3235.

number of αβ-unsubstituted coumarones. Thus, 6-hydroxy-, 6-methoxy-, and 5 : 6-dimethoxy-coumarone furnished the respective 2-trihalogenoacetyl derivatives; 4 : 6-dimethoxycoumarone gave only a low yield of 4 : 6-dimethoxy-2-trichloroacetylcoumarone and with trifluoromethyl cyanide furnished a mixture of 4 : 6-dimethoxy-2-trifluoroacetylcoumarone and larger amounts of an isomeric ketone which is formulated as 4 : 6-dimethoxy-7-trifluoroacetylcoumarone, by analogy with the production of 7-formyl-4 : 6-dimethoxycoumarone from 4 : 6-dimethoxycoumarone under the conditions of the Gattermann aldehyde synthesis (Foster and Robertson, *J.*, 1939, 921).

7-Methoxycoumarone failed to condense with trichloromethyl cyanide but with trifluoromethyl cyanide gave a ketone which is probably either the 4- or the 5-trifluoroacetyl derivative, since hydrolysis gave an acid isomeric but not identical with 7-methoxycoumarone-2-carboxylic acid.

The orientation of the trihalogenoacetylcoumarones was by hydrolysis to the corresponding carboxylic acids. Several of the coumarones used in this work are new; they were prepared by the application of standard methods as described in the Experimental section.

A comparative examination of the ultra-violet absorption spectra of these various ketones shows that a change of type (I) to (II) probably does not occur to an appreciable extent, if at all; however, the intense yellow colour exhibited by the majority of these compounds does indicate that they are probably more correctly represented as resonance structures of type (III) (cf. Whalley, *J.*, 1951, 3229).

Experimental

The Hoesch condensations with 3-methylcoumarones were carried out in the normal manner; the modified conditions necessary for the application of this reaction to αβ-unsubstituted coumarones are exemplified by the following preparation.

6-*Methoxy*-2-*trifluoroacetylcoumarone*.—Prepared by the gradual addition of a solution of 6-methoxycoumarone (Pfeiffer and Grimmer, *Ber.*, 1917, **42**, 911) (1 g.) in ether (10 ml.) to a mixture of zinc chloride (1 g.) in ether (50 ml.) and trifluoromethyl cyanide [from the amide (7 g.)] previously saturated with hydrogen chloride at 0°, 6-*methoxy*-2-*trifluoroacetylcoumarone* (1 g.) separated from light petroleum (b. p. 60—80°) in prisms, m. p. 114° (Found: C, 54·1; H, 3·6; F, 24·6. $C_{11}H_7O_3F_3$ requires C, 54·1; H, 2·9; F, 23·4%). Hydrolysis with warm 2N-sodium hydroxide gave 6-methoxycoumarone-2-carboxylic acid, identical with an authentic specimen (Will and Beck, *Ber.*, 1886, **19**, 1783).

The Hoesch Reaction with 4 : 6-*Dimethoxycoumarone and Trifluoromethyl Cyanide*.—Hydrolysis of the amorphous ketimine complex from 4 : 6-dimethoxycoumarone (Foster and Robertson, *loc. cit.*) furnished a crude product which upon sublimation at 100°/0·01 mm. gave a crystalline mixture (400 mg.). Purification from light petroleum (b. p. 60—80°) gave 4 : 6-*dimethoxy*-7(?)-*trifluoroacetylcoumarone* (200 mg.) in needles, m. p. 115° (Found: C, 52·2; H, 3·4. $C_{12}H_9O_4F_3$ requires C, 52·5; H, 3·3%). Hydrolysis furnished 7(?)-*carboxy*-4 : 6-*dimethoxycoumarone* in needles (from aqueous acetone), m. p. 207° (decomp.) (Found: C, 59·5; H, 5·0. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%).

Concentration of the petroleum mother liquors gave 4 : 6-dimethoxy-2-trifluoroacetylcoumarone (15 mg.), as yellow prisms [from light petroleum (b. p. 60—80°)], m. p. 122°. Hydrolysis readily furnished 4 : 6-dimethoxycoumarone-2-carboxylic acid, identical with an authentic specimen (Reichstein, Oppenauer, Grüssner, Hirt, Rhyner, and Glatthaar, *Helv. Chim. Acta*, 1935, **18**, 816).

5 : 6-*Dimethoxy*-3-*methyl*-2-*trifluoroacetylcoumarone*.—Prepared from 5 : 6-dimethoxy-3-methylcoumarone (Jones, Mackenzie, Robertson, and Whalley, *J.*, 1949, 562) (0·8 g.), 5 : 6-*dimethoxy*-3-*methyl*-2-*trifluoroacetylcoumarone* (1 g.) separated from light petroleum (b. p. 60—80°) in lemon-yellow prisms, m. p. 128° (Found: C, 53·9; H, 3·9. $C_{13}H_{11}O_4F_3$ requires C, 54·2; H, 3·8%). The cherry-red solution of this coumarone in concentrated sulphuric acid became deep red when warmed, whilst hydrolysis with warm 2N-sodium hydroxide rapidly gave a quantitative yield of 5 : 6-*dimethoxy*-3-*methylcoumarone*-2-*carboxylic* acid as prisms, m. p. 228° (decomp.) (from aqueous acetone) (Found: C, 60·9; H, 5·4. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%). The green solution in sulphuric acid became violet when warmed. The same acid was obtained by the cyclisation of ethyl 2-acetyl-4 : 5-dimethoxyphenoxyacetate with sodium ethoxide, in the usual manner, followed by hydrolysis of the crude ester.

5 : 6-*Dimethoxycoumarone*.—When a solution of 2-hydroxy-4 : 5-dimethoxybenzaldehyde (Head and Robertson, *J.*, 1930, 2434) (5 g.) in acetone (75 ml.) containing ethyl bromoacetate (6 g.) and potassium carbonate (15 g.) was heated under reflux for 6 hr. and the product isolated in the usual way, *ethyl 2-formyl-4 : 5-dimethoxyphenoxyacetate* (6 g.) separated as prisms (from ethanol), m. p. 129°, having a negative ferric reaction in alcohol (Found : C, 58·1; H, 6·3. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%).

Cyclisation of this phenoxy-ester (1 g.) in ethanol (25 ml.) furnished ethyl 5 : 6-dimethoxycoumarone-2-carboxylate (0·2 g.) in needles, m. p. 107° (from ethanol), having a negative ferric reaction in alcohol and hydrolysed by warm 2N-sodium hydroxide to 5 : 6-*dimethoxycoumarone-2-carboxylic acid*, which separated from acetone in needles, m. p. 244—246° (decomp.) (Found : C, 59·4; H, 5·0. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%).

2N-Sodium hydroxide (25 ml.) was added to a solution in ethanol (25 ml.) of ethyl 2-formyl-4 : 5-dimethoxyphenoxyacetate (4 g.), and 15 min. later the solution was diluted with water (100 ml.) and acidified; *2-formyl-4 : 5-dimethoxyphenoxyacetic acid* separated in quantitative yield and was purified from aqueous acetone, forming needles, m. p. 196°, having a negative ferric reaction in alcohol (Found : C, 55·1; H, 5·3. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%).

A solution of this acid (3 g.) in acetic anhydride (40 ml.) containing sodium acetate (7 g.) was refluxed for 4 hr. and then diluted with water. 5 : 6-*Dimethoxycoumarone* crystallised from aqueous methanol in needles, m. p. 59° (1·2 g.) (Found : C, 67·6; H, 5·9. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%).

5-*Hydroxy-3-methylcoumarone*.—A solution of 2 : 5-dihydroxyacetophenone (10 g.) (Morris, *J. Amer. Chem. Soc.*, 1949, **71**, 2056), benzyl bromide (12 g.), and anhydrous potassium carbonate (25 g.) in acetone (125 ml.) was refluxed for 4 hr. After isolation, *5-benzyloxy-2-hydroxyacetophenone* (12 g.) separated from aqueous methanol or light petroleum (b. p. 60—80°) in prisms, m. p. 69°, having a blue ferric reaction in alcohol (Found : C, 74·3; H, 6·1. Calc. for $C_{15}H_{14}O_3$: C, 74·4; H, 5·8%) (Bhalla, Mahal, and Venkataraman, *J.*, 1935, 868, record m. p. 70°).

The benzyl ether gave quantitatively *ethyl 2-acetyl-4-benzyloxyphenoxyacetate* which separated from light petroleum (b. p. 60—80°), in prisms, m. p. 50° (Found : C, 69·4; H, 6·1. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%). Attempts to cyclise this ester to the corresponding coumarone were unsuccessful.

Hydrolysis of this phenoxyacetate with 5% aqueous alcoholic sodium hydroxide gave a quantitative yield of *2-acetyl-4-benzyloxyphenoxyacetic acid* as prisms, m. p. 139° (from aqueous acetic acid) (Found : C, 67·7; H, 4·61. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%).

Cyclisation of this phenoxy-acid (10 g.) in boiling acetic anhydride (100 ml.) containing sodium acetate (25 g.) gave *5-benzyloxy-3-methylcoumarone* (7 g.) as prisms [from light petroleum (b. p. 40—60°)], m. p. 66° (Found : C, 80·5; H, 6·1. $C_{16}H_{14}O_2$ requires C, 80·6; H, 5·9%).

A solution of this coumarone (2 g.) in acetic acid (15 ml.) and concentrated hydrochloric acid (8 ml.) was refluxed during 45 min., and the cooled solution made alkaline with 2N-sodium hydroxide and extracted with ether. The alkaline liquors were then acidified and extracted with ether, and the washed and dried extract evaporated to furnish *5-hydroxy-3-methylcoumarone* (0·6 g.), which was purified by vacuum sublimation (80°/0·01 mm.), forming prisms, m. p. 92° (Found : C, 73·1; H, 5·8. $C_9H_8O_2$ requires C, 73·0; H, 5·4%).

5-*Methoxy-3-methylcoumarone*.—Prepared from 2-hydroxy-5-methoxyacetophenone (Robinson and Smith, *J.*, 1926, 392) (3 g.) in boiling acetone (50 ml.) containing ethyl bromoacetate (3·2 g.) and potassium carbonate (7 g.), *ethyl 2-acetyl-4-methoxyphenoxyacetate* (4·5 g.) separated from light petroleum in prisms, m. p. 69° (Found : C, 61·9; H, 6·3. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%).

Cyclisation of this keto-ester (2 g.) in ethanol (25 ml.) containing sodium ethoxide [from sodium (0·2 g.) and alcohol (10 ml.)] furnished *ethyl 5-methoxy-3-methylcoumarone-2-carboxylate* in prisms, m. p. 105° (Found : C, 66·7; H, 6·1. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%). The green solution in cold, concentrated sulphuric acid became cherry-red when warmed. Hydrolysis gave the corresponding *acid* as prisms (from aqueous acetone), m. p. 210° (Found : C, 64·0; H, 5·3. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). Methylation with diazomethane furnished methyl 5-methoxy-3-methylcoumarone-2-carboxylate, identical with the previously prepared specimen.

Hydrolysis of ethyl 2-acetyl-4-methoxyphenoxyacetate readily gave a quantitative yield of the corresponding acid as needles, m. p. 140°, from aqueous acetone (Found : C, 59·0; H, 5·4. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%) (Graffenreid and von Kostanecki, *Ber.*, 1910, **43**, 2155, record m. p. 144—145°).

Cyclisation of this phenoxy-acid (2 g.) in boiling acetic anhydride (10 ml.) containing sodium

acetate (5 g.) furnished 5-*methoxy*-3-*methylcoumarone* (1·5 g.), b. p. 105°/0·05 mm. (Found: C, 73·9; H, 6·3. $C_{10}H_{10}O_2$ requires C, 74·1; H, 6·2%).

5-*Methoxycoumarone*.—When a solution of 2-hydroxy-5-methoxybenzaldehyde (6·5 g.) (Rubenstein, *J.*, 1925, 1998) and chloroacetic acid (15 g.) in water (50 ml.) containing potassium hydroxide (15 g.) was warmed on the steam-bath during 70 min., cooled, and acidified, a crystalline precipitate separated. Recrystallisation from aqueous acetone furnished 2-*formyl*-4-*methoxyphenoxyacetic acid* (7 g.) in prisms, m. p. 155—156°, having a negative ferric reaction in alcohol and instantly soluble in 2N-sodium hydrogen carbonate (Found: C, 56·8; H, 5·2. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%).

This phenoxy-acid (7 g.) furnished 5-methoxycoumarone (2·5 g.), b. p. 160°/14 mm. (Stoermer, *Annalen*, 1900, **312**, 335), which was insoluble in 2N-sodium hydroxide; its reddish-green solution in cold concentrated sulphuric acid became deep red when warmed.

Prepared from 2-hydroxy-5-methoxybenzaldehyde (5 g.), in the usual way, ethyl 2-formyl-4-methoxyphenoxyacetate was obtained in quantitative yield. Cyclisation of this liquid ester (10 g.) with sodium ethoxide [from sodium (1 g.)] in alcohol (25 ml.) furnished *ethyl* 5-*methoxycoumarone*-2-*carboxylate* (1·5 g.) as prisms (from aqueous ethanol), m. p. 62° (Found: C, 65·2; H, 5·9. $C_{12}H_{12}O_4$ required C, 65·4; H, 5·5%). Hydrolysis gave 5-*methoxycoumarone*-2-*carboxylic acid*, needles (from aqueous acetone), m. p. 217° (Found: C, 62·5; H, 4·2. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%), identical with the product obtained by the hydrolysis of 5-methoxy-2-trifluoroacetylcoumarone.

7-*Methoxycoumarone*.—A mixture of *o*-vanillin (10 g.), chloroacetic acid (15 g.), potassium hydroxide (15 g.), and water (75 ml.) was warmed on the steam-bath for 1½ hr., cooled, diluted with water (100 ml.), and acidified, and the crystalline solid which separated was dissolved in ether (200 ml.). Extraction of this ethereal solution with 2N-sodium hydrogen carbonate and acidification of the extract furnished 2-*formyl*-6-*methoxyphenoxyacetic acid* (6 g.) in prisms, m. p. 119° (from aqueous acetone) (Found: C, 57·2; H, 5·1. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%).

A solution of this phenoxy-acid (6·5 g.) in acetic anhydride (50 ml.) containing sodium acetate (10 g.) was refluxed for 5 hr. (shorter periods gave much uncyclised phenoxy-acid), and after isolation and separation from starting material 7-methoxycoumarone (2·2 g.) was obtained, b. p. 140°/16 mm. (Reichstein *et al.*, *loc. cit.*, record b. p. 68°/0·4 mm.).

The Hoesch Reaction with 7-*Methoxycoumarone and Trifluoromethyl Cyanide*.—7-Methoxycoumarone (1 g.) furnished 7-*methoxy*-x-*trifluoromethylcoumarone* (0·8 g.), as prisms, m. p. 110°, from light petroleum (b. p. 60—80°) (Found: C, 53·6; H, 3·3. $C_{11}H_7O_3F_3$ requires C, 54·1; H, 2·9%).

Hydrolysis of this ketone furnished 7-*methoxycoumarone*-x-*carboxylic acid* as needles (from aqueous acetone), m. p. 227° (Found: C, 62·6; H, 4·5. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%). The mixed m. p. with an authentic specimen of 7-methoxycoumarone-2-carboxylic acid (Reichstein *et al.*, *loc. cit.*) was *ca.* 200°.

7-*Methoxy*-3-*methylcoumarone*.—Prepared from 2-hydroxy-3-methoxyacetophenone, ethyl 2-acetyl-6-methoxyphenoxyacetate was obtained in quantitative yield as a pale yellow oil which was cyclised to give *ethyl* 7-*methoxy*-3-*methylcoumarone*-2-*carboxylate* (0·7 g.) which separated from aqueous acetone in needles, m. p. 70° (Found: C, 67·1; H, 6·3. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%).

Hydrolysis of this ester furnished a quantitative yield of 7-*methoxy*-3-*methylcoumarone*-2-*carboxylic acid* in needles, m. p. 216° (from aqueous acetone) (Found: C, 64·1; H, 4·9. $C_{11}H_{10}O_4$ requires C, 64·5; H, 5·3%).

Ethyl 2-acetyl-6-methoxyphenoxyacetate was hydrolysed quantitatively with warm dilute aqueous–alcoholic sodium hydroxide to give the *acid* in needles, m. p. 122° (from aqueous acetone) (Found: C, 59·1; H, 5·4. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%). When a solution of this acid (5 g.) in acetic anhydride (25 ml.) containing fused sodium acetate (15 g.) was refluxed for 3 hr. and then poured into water (300 ml.), a dark crystalline solid slowly separated (24 hr.). The dried product was distilled to give 7-*methoxy*-3-*methylcoumarone* (3 g.), b. p. 80°/0·01 mm., m. p. 46°; it was very soluble in the usual organic solvents (Found: C, 73·9; H, 6·3. $C_{10}H_{10}O_2$ requires C, 74·1; H, 6·2%).

7-*Methoxy*-3-*methyl*-2-*trifluoroacetylcoumarone*.—Purification from light petroleum (b. p. 40—60°) of the product from 7-methoxy-3-methylcoumarone gave 7-*methoxy*-3-*methyl*-2-*trifluoroacetylcoumarone* (0·5 g.) in stout prisms, m. p. 131° (Found: C, 55·8; H, 3·5. $C_{12}H_9O_3F_3$ requires C, 56·0; H, 3·5%). Hydrolysis readily furnished 7-methoxy-3-methylcoumarone-2-carboxylic acid, identical with an authentic specimen.

Concentration of the light petroleum mother-liquors furnished 7-*methoxy*-3-*methyl*-x-*tri*-

fluoroacetylcoumarone (0·4 g.) (Found: C, 55·8; H, 3·6%), which was hydrolysed to **7-*methoxy*-3-*methylcoumarone*-x-*carboxylic acid***, needles, m. p. 216° (from aqueous acetone) (Found: C, 64·5; H, 5·0. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). The pale yellow solution in sulphuric acid became violet when warmed, and the mixed m. p. with the 2-carboxylic acid was *ca.* 175°.

7-Methoxy-3-methylcoumarone failed to undergo the Gattermann aldehyde condensation and was recovered.

The absorption spectra were determined in 95% ethanol solution on a Carey Self-recording Spectrophotometer, Model 11, by courtesy of Smith, Kline, and French Laboratories, Philadelphia.

UNIVERSITY OF LIVERPOOL. [*Received, June 20th,* 1953.]

700. *The Photomutarotation of (−)-2-Chloro-2-nitrosocamphane.*

By A. J. N. HOPE and STOTHERD MITCHELL.

When (−)-2-chloro-2-nitrosocamphane is exposed to either red or ultraviolet light, the rotatory-dispersion curve is modified and shifted slightly towards longer wave-lengths. The absorption curve is displaced in a similar manner. These effects are due to a simple isomeric change, and probable configurations are assigned to the two forms of the compound.

IN a previous paper (Mitchell, Watson, and Dunlop, *J.*, 1950, 3440) it was shown that irradiation of an alcoholic solution of (−)-2-chloro-2-nitrosocamphane with red light produced a gradual inversion of the Cotton effect. From further work we now conclude that under the influence of light the positions of the chlorine and nitroso-groups on $C_{(2)}$ are interchanged. When photoisomerisation is accompanied by a change in optical rotation, as in the present case, the process may be called "photomutarotation."

Specimens of 2-chloro-2-nitrosocamphane, prepared by the action of chlorine on camphor oxime hydrochloride, have $[\alpha]_{6000} \simeq +700°$. This value is not raised appreciably by chromatography on a number of adsorbants (which are effective for the purpose of purification), but passage through activated alumina gives a product with $[\alpha]_{6000} = +964°$. This increase in rotation can be explained by postulating two isomeric forms one of which is converted into the other (of higher rotation) during adsorption on alumina.* The rotatory dispersion curve (Mitchell *et al.*, *loc. cit.*) shows that (−)-2-chloro-2-nitrosocamphane has been produced.

An alcoholic solution of this material was irradiated with red light in the hope of isolating the mutarotated product, but on removal of the solvent an intractable gum remained. When a thin layer of the solid was irradiated *in vacuo*, however, the product could be purified by chromatography on sugar-charcoal. After further irradiation and purification $[\alpha]_{6060}$ became constant at −508°. Analysis confirmed that the materials

TABLE 1. *Rotatory dispersion of (+)-2-chloro-2-nitrosocamphane in alcohol.*

$c = 1·408$ g./100 ml.; $l = 2·5$ cm.; $t = 18°$.

λ, Å	5200	5400	5500	5600	5700	5800	5900	6000	6100	6200	6300
α, °	−1·01	−1·18	−1·27	−1·38	−1·50	−1·59	−1·68	−1·74	−1·78	−1·70	−1·60
[α], °	−287	−335	−361	−392	−426	−452	−477	−494	−506	−483	−454

λ, Å	6400	6500	6600	6700	6800	6900	7000	7100	7200	7300	7400
α, °	−1·45	−1·26	−1·04	−0·46	+0·26	+0·79	+1·16	+1·39	+1·50	+1·44	+1·33
[α], °	−412	−358	−295	−131	+ 74	+224	+330	+395	+426	+409	+378

before and after irradiation were indeed isomeric. Rotatory-dispersion data are given in Table 1, and from these it is apparent that the rotatory dispersion curve is an inverted form of the original. The new isomer may therefore be called (+)-2-chloro-2-nitrosocamphane.

* Several other examples of isomerisation on polar adsorbants are known (cf. Gillam and El Ridi, *Biochem. J.*, 1936, **30**, 1735; Gallaway and Murray, *J. Amer. Chem. Soc.*, 1948, **70**, 2584).

The anomalies in rotatory dispersion for the two forms can now be compared:

	Short-wave maxima	Reversal	Long-wave maxima
(−)-form	$[\alpha] = +964°$ at 6000 Å	6700 Å	$[\alpha] = -946°$ at 7100 Å
(+)-form	$[\alpha] = -508°$ at 6060 Å	6760 Å	$[\alpha] = +430°$ at 7160 Å

Thus, besides being inverted, the rotatory-dispersion curve for the (+)-form is displaced about 60 Å towards longer wave-lengths.

Absorption spectra for alcoholic solutions of the two forms are shown in Fig. 1. The curves are very similar but are separated by some 50—60 Å. In each case two regions of absorption are apparent; the band in the red is due to the nitroso-group, and the ultra-violet absorption to the presence of chlorine.

Since red light causes photomutarotation it appeared likely that the same effect might be produced by ultra-violet light, and this was tested experimentally by using a mercury lamp (with a Chance OX 7 filter to eliminate the green and yellow lines). The results are set out in Table 2, which shows the fall in rotation with time. In this case, the rate of photolysis is greater than that of photomutarotation so that the rotation does not pass through a minimum value as when red light was employed. We have corrected for

FIG. 1.

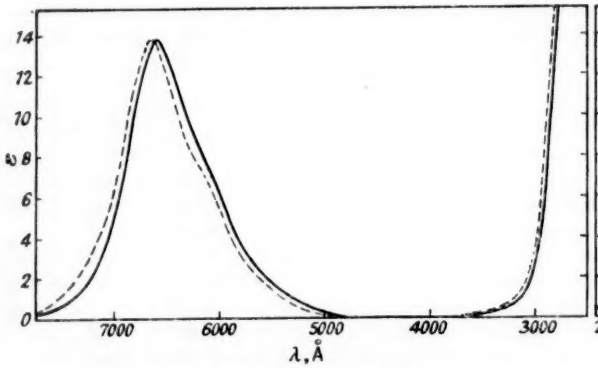
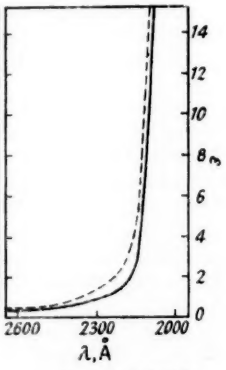


FIG. 2.



photolysis by making a photoelectric estimation of concentration at 6625 Å (for which both the absorption curves in Fig. 1 have the same value of ε). This enabled us to calculate specific rotations which show the true course of mutarotation.

TABLE 2. *Irradiation of an alcoholic solution of* (−)-2-*chloro*-2-*nitrosocamphane with ultra-violet light.*

Concn. (c_0) = 1·888 g./100 ml. in a 1-cm. cell.

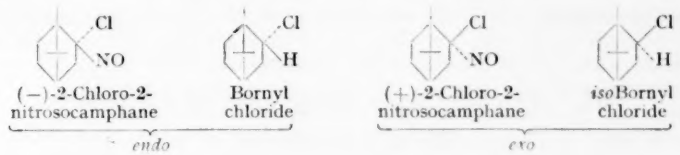
$k = \log I_0/I$ at 6625 Å, and $[\alpha] = 1000\alpha/c$ where $c = c_0 \times k/k_0$.

Min.	0	5	15	30	45	60	90	135	180	210
α_{6030}, °	1·80	1·68	1·51	1·25	1·04	0·85	0·56	0·33	0·17	0·11
k	1·27	1·22	1·16	1·05	0·95	0·86	0·71	0·54	0·40	0·32
$[\alpha]_{6030}$, °	953	926	876	801	736	665	531	411	286	231

We also constructed an absorption curve after 135 min. of irradiation with ultra-violet light and found on comparing it with the original that the shift characteristic of photo-mutarotation had taken place.

When 2-chloro-2-nitrosocamphane prepared from (±)-camphor was exposed to red light no observable rotation developed at any stage in the reaction, but the absorption curve of the final material was found to be displaced 50—60 Å to longer wave-lengths, showing that both enantiomorphic forms had mutarotated, but in opposite directions and at exactly the same rate.

Having shown that (−)-2-chloro-2-nitrosocamphane isomerises under the influence of light, it remained to assign configurations to the two isomeric forms.* The compounds of known configuration most closely related to them are bornyl chloride and *iso*bornyl chloride. We have examined the absorption spectra of these two compounds (in hexane) as far into the ultra-violet as our instrument would permit, and they are given in Fig. 2. The difference in position of the absorption curves here is closely analogous to that shown in Fig. 1 for the two chloro-nitroso-isomers under investigation. Accordingly we suggest that the following pairs have similar configurations. The usual steric conventions are employed.



(−)-2-Chloro-2-nitrosocamphane — Bornyl chloride (*endo*)

(+)-2-Chloro-2-nitrosocamphane — *iso*Bornyl chloride (*exo*)

Experimental

(−)-2-*Chloro*-2-*nitrosocamphane*.—Camphor oxime hydrochloride in dry ether was chlorinated according to Mitchell *et al.* (*loc. cit.*) but with the following modifications. After removal of the ether, the blue solid was dissolved in the minimum volume of light petroleum, and the unchanged oxime hydrochloride filtered off. The filtrate was transferred to a column of sugar charcoal (50 × 2·5 cm.), and the blue band eluted with the same solvent. This treatment yielded a product with $[\alpha]_{6000} = +707°$; $\varepsilon_{max.} = 13·6$; m. p. 145—146° (decomp.). Passage of this material through a column (50 × 2·5 cm.) of Light's alumina (activated at 200° for 4 hr.) gave a product with $[\alpha]_{6000} = +803°$; $\varepsilon_{max.} = 13·7$ (for $\lambda = 6600$ Å); m. p. 145—146° (decomp.). Re-adsorption on alumina raised $[\alpha]_{6000}$ to +964° while the absorption maximum and m. p. remained unchanged. All operations were carried out in diffuse light.

(+)-2-*Chloro*-2-*nitrosocamphane*.—A cylindrical 200-ml. cell, containing (−)-2-chloro-2-nitrosocamphane (0·25 g.), was placed vertically on one end and evacuated to 0·1 mm. The bottom surface was kept at 30—40° on a warm plate and the upper end cooled to −180° by contact with a brass vessel containing liquid air. The material sublimed on the cold upper surface in the course of 30 min., forming a thin 15-sq. cm. film. The cell was irradiated with light from a carbon arc, the condensed beam first passing through a circulating water filter and a piece of infra-red glass (Chance ON 20). Irradiation was continued for 30 min., during which time the cell was reversed frequently. Thereafter, the vacuum was released and the solution of material in light petroleum chromatographed on sugar-charcoal (25 × 1 cm.). The product had $[\alpha]_{6060} = -438°$; $\varepsilon_{max.} = 13·7$ (for $\lambda = 6650$ Å); m. p. 140—141° (decomp.). This procedure was repeated several times and the products were combined and used as starting material for the second stage, which consisted of irradiation and purification as before. This gave (+)-2-*chloro*-2-*nitrosocamphane* with $[\alpha]_{6060} = -508°$; $\varepsilon_{max.} = 13·8$; m. p. 140—141° (decomp.). Continued processing by these methods did not change the rotation further (Found: C, 59·8; H, 7·6; N, 6·7. $C_{10}H_{16}ONCl$ requires C, 59·7; H, 7·9; N, 6·9%).

Ultra-violet Irradiation of (−)-2-*chloro*-2-*nitrosocamphane*.—A solution of (−)-2-chloro-2-nitrosocamphane (1·888 g./100 ml.) in oxygen-free alcohol was contained in a stoppered Vitreosil cell (1 cm.) with strain-free end-pieces. This was irradiated with a Kromayer water-cooled mercury lamp, a Chance OX 7 filter being used.

Polarimetric and absorption measurements were made at various times. For the latter a special carrier was constructed enabling the cell to be fitted directly into the spectrophotometer.

Inactive 2-*Chloro*-2-*nitrosocamphane*.—The preparation and purification were similar to those for (−)-2-chloro-2-nitrosocamphane. After chromatography on sugar-charcoal, the product was found to have absorption maximum and m. p. identical with the above compound. All operations were carried out in diffuse light.

Bornyl Chloride.—Commercial "pinene hydrochloride" (22·5 g.) was crystallised twice from "AnalaR" amyl alcohol (18·5 g.). The crystals were washed with methyl alcohol (2 ml.), and

* It should be noted that we have no means of establishing that our separation of the two isomeric forms is complete. We can say, however, that the (−)-form has the highest maximum rotation obtainable by adsorption on alumina, and the (+)-form has the lowest minimum rotation that irradiation with red light can produce.

trituration with this solvent removed the remaining traces of amyl alcohol. The product, dried *in vacuo* over sodium hydroxide, had m. p. 132—133°, $[\alpha]_D = +25{\cdot}9°$ (*c*, 1·004 in EtOH).

iso*Bornyl Chloride*.—This is best prepared by the rearrangement of camphene hydrochloride under carefully controlled conditions according to Meerwein and van Emster (*Ber.*, 1922, **55**, 2526), who claim 99·6% purity. Our product had m. p. 159—160°.

Optical Measurements.—Rotation readings were taken with a Hilger (triple-field) polarimeter in conjunction with a Winkel–Zeiss monochromator and a 12-v projection lamp. Absorption measurements were made on a Unicam SP. 500 spectrophotometer.

The microanalyses were carried out by Mr. J. M. L. Cameron and Miss M. W. Christie.

University of Glasgow. [*Received, July 1st*, 1953.]

---

701. *Friedel–Crafts Acetylation of Chrysene.*

By W. Carruthers.

Reaction of chrysene with acetyl chloride and aluminium chloride in carbon disulphide–acetyl chloride or in nitrobenzene yields a mixture of 2-, 4-, and 5-acetylchrysenes. In methylene chloride only 2-acetylchrysene is produced. 2-, 4-, and 5-Ethylchrysenes are readily obtained by reduction of the corresponding acetyl compounds.

Although several methods have been elaborated for the synthesis of alkylchrysenes (see, for example, Newman, *J. Amer. Chem. Soc.*, 1938, **60**, 2947; 1940, **62**, 870; Bachmann and Struve, *J. Org. Chem.*, 1939, **4**, 456; 1940, **5**, 416), all are laborious. A more direct route to some at least of these compounds would be afforded by reduction of the ketones known to be produced by Friedel–Crafts acylation of chrysene. The orientation of these ketones, however, is not securely established, and the present investigation was designed to identify the acetylation products of chrysene.

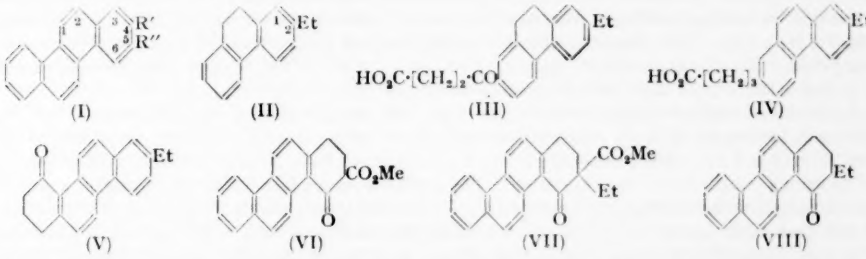
Reaction of chrysene with acetyl chloride and aluminium chloride in a mixture of carbon disulphide and acetyl chloride was studied by Funke and Müller (*J. pr. Chem.*, 1936, **144**, 242), who isolated two ketones which they regarded as 1- and 2-acetylchrysenes. Newman (*loc. cit.*), however, showed that the alleged 1-isomer could not in fact have this orientation, for the ethylchrysene obtained from it by reduction was different from 1-ethylchrysene which he synthesised by an unambiguous route. It was suggested by Bergmann and Eschinazi (*J. Amer. Chem. Soc.*, 1943, **65**, 1413) that this ketone was actually 4-acetylchrysene, on the basis of its high melting-point.

In the present work, reaction in a mixture of carbon disulphide and acetyl chloride as described by Funke and Müller (*loc. cit.*) gave three ketonic products, isolated by fractional crystallisation. Two of these were identical with the compounds found by Funke and Müller (*loc. cit.*); the third was apparently overlooked by these authors. 2-Acetylchrysene was identified by Clemmensen reduction to the known 2-ethylchrysene and by oxidation to the known 2-carboxylic acid. The so-called "1-acetylchrysene" was shown to be 4-acetylchrysene, since on Clemmensen reduction it afforded 4-ethylchrysene which was identified through its unequivocal synthesis as described below. Because of its low solubility, this isomer was readily isolated from the reaction mixture in about 15% yield. The third isomer, obtained in approximately 10% yield, was identified as 5-acetylchrysene by reduction to 5-ethylchrysene, which was also synthesised. A similar mixture of the 2-, 4-, and 5-isomers was obtained when the reaction was conducted in nitrobenzene solution. In methylene chloride, however, only 2-acetylchrysene was produced, in high yield (75%). This is fortunate, for the 2-isomer is the most difficult to isolate from the reactions in nitrobenzene and carbon disulphide.

Chrysene thus resembles phenanthrene (Mosettig and van de Kamp, *J. Amer. Chem. Soc.*, 1930, **52**, 3704) in reacting to a considerable extent in a side ring during Friedel–Crafts acetylation in nitrobenzene and carbon disulphide. This is in accord with Baddeley's observation (*J.*, 1949, S 1, 99) that use of nitrobenzene as solvent in acetylation of naph-

thalene leads to greater reaction at the less reactive, but sterically less hindered, β-position, than occurs in methylene chloride.

The starting material for the synthesis of 4-ethylchrysene was 2-ethyl-9 : 10-dihydrophenanthrene (II), itself obtained from the corresponding acetyl compound (Burger and Mosettig, *J. Amer. Chem. Soc.*, 1936, **58**, 1857) by Huang-Minlon reduction (*J. Amer. Chem. Soc.*, 1946, **68**, 2487). Condensation of (II) with succinic anhydride and aluminium chloride in nitrobenzene afforded a keto-acid which, by analogy with the similar reaction of 9 : 10-dihydrophenanthrene (Burger and Mosettig, *J. Amer. Chem. Soc.*, 1937, **59**, 1302), is regarded as (III). Reduction of this by the Huang-Minlon procedure (*loc. cit.*) yielded the corresponding butyric acid, the methyl ester of which was dehydrogenated by heating it with palladium. The product was hydrolysed, and the resulting ethylphenanthrylbutyric acid (IV) cyclised by treatment of its acid chloride with stannic chloride, yielding 10-ethyl-3 : 4 : 5 : 6-tetrahydro-6-oxochrysene (V) almost exclusively (compare Bachmann and Struve, *J. Org. Chem.*, 1939, **4**, 456). Clemmensen reduction of the carbonyl group, followed by dehydrogenation of the crude product with palladium, gave 4-ethylchrysene (I; R′ = Et, R″ = H).



(I) (II) (III) (IV) (V) (VI) (VII) (VIII)

5-Ethylchrysene was prepared from methyl 3 : 4 : 5 : 6-tetrahydro-6-oxochrysene-5-carboxylate (VI) (Bachmann and Struve, *J. Org. Chem.*, 1940, **5**, 416). Reaction of this compound with ethyl iodide in the presence of sodium methoxide furnished the expected product (VII) and hence, by boiling it with hydrochloric acid, the ketone (VIII). 5-Ethylchrysene was readily obtained from this ketone by Clemmensen reduction, and dehydrogenation of the resultant crude tetrahydrochrysene derivative with palladium.

Experimental

Acetylation of Chrysene.—(a) *In carbon disulphide.* Acetyl chloride (60 c.c.) and powdered aluminium chloride (10 g.) were added to a stirred suspension of finely powdered chrysene (10 g.) in carbon disulphide (250 c.c.). After 2 days the mixture was boiled for 6 hr. The solvent was removed, and ice and hydrochloric acid were added. The dried residue was boiled with carbon tetrachloride (250 c.c.) and filtered hot. The crystals which separated on cooling were combined with the residue, and the whole crystallised from benzene–ethanol (charcoal), whereby 4-*acetylchrysene* (1·6 g.) was obtained as needles, m. p. 252—253° (Found: C, 88·7; H, 5·5. $C_{20}H_{14}O$ requires C, 88·8; H, 5·2%). The carbon tetrachloride solution was concentrated to 50 c.c., separated from a little 4-acetylchrysene, and set aside at 0° for several days. The crystals were collected and crystallised from benzene–light petroleum (b. p. 60—80°), yielding 5-*acetylchrysene* (1·0 g.) as needles, m. p. 159° (Found: C, 89·1; H, 5·4%). Further concentration of the mother liquors, and fractional crystallisation of the material obtained from carbon tetrachloride and from ethanol yielded 2-acetylchrysene (0·5 g.), m. p. 141° (lit. 144°), and a further small amount of 5-acetylchrysene.

(b) *In nitrobenzene.* Aluminium chloride (3·4 g.) and acetyl chloride (1·8 c.c.) were dissolved in nitrobenzene (15 c.c.), and to the stirred solution, at 0°, was added a suspension of finely powdered chrysene (5 g.) in nitrobenzene (35 c.c.). After 1 hr. the temperature was raised to 35—40°, and stirring continued for 4 hr. Next morning, ice and hydrochloric acid were added and nitrobenzene removed in steam. The washed and dried crude product (5·8 g.) was extracted with boiling ethanol (4 × 40 c.c.), and the combined extracts set aside. The crystals (1·7 g.) which separated were combined with the residue and crystallised from benzene (charcoal), giving 4-acetylchrysene (0·7 g.) as needles, m. p. 254°. The alcohol liquors were evaporated

and the residue crystallised from carbon tetrachloride as described above, yielding 2- and 5-acetylchrysene, in yields of 0·6 g. and 0·5 g., respectively.

(c) *In methylene chloride.* A suspension of finely powdered chrysene (5 g.) in methylene chloride (25 c.c.) was added to a stirred solution of aluminium chloride (3·4 g.) and acetyl chloride (1·8 c.c.) in methylene chloride (100 c.c.) at 0°. Stirring was continued for a further 2 hr. at 35—40°. Next morning, ice and hydrochloric acid were added, and methylene chloride was distilled off. The crude product (5·7 g.), after being washed and dried, was adsorbed in benzene on alumina. Elution with benzene first removed a small amount of chrysene. 2-Acetylchrysene was then obtained and after crystallisation from benzene–ethanol formed needles (3·9 g.), m. p. 142—143°. No other product was detected.

Oxidation of 2-, 4-, *and* 5-*Acetylchrysenes.*—The acetylchrysenes were oxidised to the carboxylic acids with sodium hypoiodite, by the method described by Fuson and Tulloch (*J. Amer. Chem. Soc.*, 1934, **56**, 1638). *Chrysene-4-carboxylic acid* formed clusters of fluffy pale yellow needles, m. p. 325—327° (decomp.), from dioxan (Found: C, 83·6; H, 4·6. $C_{19}H_{12}O_2$ requires C, 83·8; H, 4·4%). The *methyl* ester, from the acid and diazomethane, crystallised from benzene in pale yellow plates, m. p. 219° (Found: C, 83·7; H, 4·9. $C_{20}H_{14}O_2$ requires C, 83·9; H, 4·9%). *Chrysene-5-carboxylic acid* was obtained from aqueous dioxan as pale yellow needles, m. p. 295° (decomp. with sintering at 285°) (Found: C, 84·1; H, 4·6%). Treatment of the acid with diazomethane afforded the *methyl* ester as plates, m. p. 146—147° (Found: C, 83·7; H, 4·7%). Chrysene-2-carboxylic acid gave pale yellow needles, m. p. 305° (decomp.), from dioxan (Funke and Müller, *loc. cit.*, give m. p. 308°). The *methyl* ester formed plates, m. p. 143—144°, from methanol–benzene (Found: C, 83·6; H, 4·9%).

2-*Ethyl*-9 : 10-*dihydrophenanthrene* (II).—2-Acetyl-9 : 10-dihydrophenanthrene (1·3 g.), potassium hydroxide (0·8 g.), and hydrazine hydrate (90%; 1 c.c.) in diethylene glycol (9 c.c.) were boiled for 1 hr. The temperature was then raised to 190—200° by distilling off the water, and refluxing continued for 3 hr. further. The cooled mixture was diluted with water, acidified, and extracted with benzene. The washed and dried extract was evaporated and the residual oil distilled over sodium. 2-*Ethyl*-9 : 10-*dihydrophenanthrene* was collected as a colourless oil (1·1 g.), b. p. 130°/0·4 mm. (Found: C, 92·4; H, 7·5. $C_{16}H_{16}$ requires C, 92·3; H, 7·7%).

Reaction of 2-*Ethyl*-9 : 10-*dihydrophenanthrene with Succinic Anhydride.*—To an ice-cold solution of the above hydrocarbon (1·4 g.) and succinic anhydride (0·7 g.) in nitrobenzene (3 c.c.) was added a suspension of powdered aluminium chloride (1·8 g.) in nitrobenzene (5 c.c.). The mixture was allowed to warm to room temperature overnight and decomposed with ice and hydrochloric acid. Nitrobenzene was removed in steam, and the residue extracted with sodium carbonate solution. Acidification yielded a brown powder (1·7 g.); after crystallisation from acetic acid and from benzene–light petroleum (b. p. 60—80°) β-(7-*ethyl*-9 : 10-*dihydro*-2-*phenanthroyl*)*propionic acid* (III) formed blades, m. p. 163—164° (Found: C, 78·2; H, 6·6. $C_{20}H_{20}O_3$ requires C, 77·9; H, 6·5%).

γ-(7-*Ethyl*-9 : 10-*dihydro*-2-*phenanthryl*)*butyric Acid.*—A solution of the keto-acid (1·0 g.), sodium hydroxide (0·5 g.), and hydrazine hydrate (90%; 1 c.c.) in diethylene glycol (10 c.c.) was refluxed for 1 hr. The temperature of the solution was then raised to 190—200° by distilling off some of the water, and refluxing continued for 3 hr. more. The cooled solution was diluted with water, acidified, and extracted with benzene. The *acid* (0·95 g.) was obtained on evaporation of the solvent; it crystallised from aqueous ethanol in plates, m. p. 122—123° (Found: C, 81·5; H, 7·3. $C_{20}H_{22}O_2$ requires C, 81·6; H, 7·5%).

γ-(7-*Ethyl*-2-*phenanthryl*)*butyric Acid* (IV).—The dihydrophenanthrylbutyric acid (0·6 g.) was converted into its methyl ester by treatment with diazomethane. The crude ester was dehydrogenated directly by heating it at 260—270° with palladium–charcoal (10%; 0·4 g.) in carbon dioxide. The product was extracted with benzene and hydrolysed with aqueous-alcoholic potassium hydroxide. The crude acid obtained on acidification (0·48 g.) was crystallised from dilute acetic acid and from benzene–*n*-hexane, yielding γ-(7-*ethyl*-2-*phenanthryl*)-*butyric acid* (0·2 g.) as plates, m. p. 172—173° (Found: C, 81·9; H, 7·0. $C_{20}H_{20}O_2$ requires C, 82·2; H, 6·9%).

10-*Ethyl*-3 : 4 : 5 : 6-*tetrahydro*-6-*oxochrysene* (V).—A suspension of γ-(7-ethyl-2-phenanthryl)-butyric acid (0·2 g.) in ether (5 c.c.) was treated with thionyl chloride (0·4 c.c.) and a few drops of pyridine. After 2 hr., ether and excess of thionyl chloride were removed, and the acid chloride was dissolved in benzene (5 c.c.). To this ice-cold solution was added, with shaking, a solution of stannic chloride (0·3 c.c.) in benzene (1 c.c.). The solution was allowed to warm to room temperature during 3 hr., and ice and hydrochloric acid were added. The benzene layer was separated, washed, dried, and passed through alumina. Development with benzene

afforded a main orange band which yielded crystals (140 mg.); crystallisation from ethanol afforded 10-*ethyl*-3 : 4 : 5 : 6-*tetrahydro*-6-*oxochrysene* as plates, m. p. 138—139° (Found: C, 87·3; H, 6·4. $C_{20}H_{18}O$ requires C, 87·6; H, 6·6%).

4-*Ethylchrysene* (I; R′ = Et, R″ = H).—(*a*) A mixture of the above ketone (200 mg.), amalgamated zinc (1 g.), concentrated hydrochloric acid (5 c.c.), water (1 c.c.), acetic acid (2 c.c.), and toluene (1·5 c.c.) was boiled for 48 hr., the cooled mixture extracted with benzene, and the extract washed, dried, and evaporated. The solid was dehydrogenated at 280—300° for 30 min. with palladium–charcoal (30%; 200 mg.) in carbon dioxide. The product was extracted with benzene and, after purification by chromatography, gave 4-*ethylchrysene* as plates (140 mg.), m. p. 237—238° (from benzene) (Found: C, 93·5; H, 6·5. $C_{20}H_{16}$ requires C, 93·7; H, 6·3%). The 2 : 7-dinitroanthraquinone *complex* formed fluffy bright-red needles, m. p. 238° from benzene (Found: N, 5·1. $C_{34}H_{22}O_6N_2$ requires N, 5·1%).

(*b*) 4-Acetylchrysene (100 mg.), amalgamated zinc (2 g.), hydrochloric acid (10 c.c.), water (5 c.c.), acetic acid (2 c.c.), and toluene (2 c.c.) were boiled for 24 hr. The product was obtained in the usual manner, and purified by chromatography on alumina in benzene. Crystallisation from benzene–ethanol gave 4-ethylchrysene (60 mg.), m. p. 236—237° alone or mixed with the material obtained as above.

Methyl 5-*Ethyl*-3 : 4 : 5 : 6-*tetrahydro*-6-*oxochrysene*-5-*carboxylate* (VII).—Methyl 3 : 4 : 5 : 6-tetrahydro-6-oxochrysene-5-carboxylate (140 mg.) (Bachmann and Struve, *loc. cit.*) in benzene (3 c.c.) was added to a solution of sodium methoxide [from sodium (45 mg.) and methanol (1·5 c.c.)], and the solution boiled for 2 hr. Ethyl iodide (0·5 c.c.) was added and boiling continued for 30 min., followed by addition of more ethyl iodide (1 c.c.). Next morning the product was obtained as a yellow gum (158 mg.) by acidification with dilute acetic acid and extraction with benzene. It was purified by chromatography in benzene solution on silica gel, and then afforded the *keto-ester* as needles, m. p 74° (from methanol) (Found: C, 79·2; H, 5·9. $C_{22}H_{20}O_3$ requires C, 79·5; H, 6·1%).

5-*Ethyl*-3 : 4 : 5 : 6-*tetrahydro*-6-*oxochrysene* (VIII).—A mixture of the keto-ester (110 mg.), acetic acid (3 c.c.), and concentrated hydrochloric acid (1 c.c.) was boiled for 4 hr., and the cooled mixture was then diluted with water and extracted with benzene. Evaporation of the washed and dried extract yielded a gum which was chromatographed in benzene on alumina. 5-*Ethyl*-3 : 4 : 5 : 6-*tetrahydro*-6-*oxochrysene* was obtained as prisms (98 mg.), m. p. 62—63° (from hexane) (Found: C, 87·5; H, 6·4. $C_{20}H_{18}O$ requires C, 87·5; H, 6·6%).

5-*Ethylchrysene* (I; R′ = H, R″ = Et).—(*a*) A mixture of the above ketone (82 mg.), amalgamated zinc (1 g.), concentrated hydrochloric acid (4 c.c.), acetic acid (1 c.c.), and xylene (1 c.c.) was boiled for 20 hr. The product was extracted with benzene and recovered from the washed and dried extract as a brown gum (80 mg.) which was dehydrogenated with palladium–charcoal (30%; 60 mg.) at 280—300° for 30 min. in an atmosphere of carbon dioxide. The cooled mixture was extracted with benzene and the dark product (35 mg.) adsorbed on alumina. Elution with benzene afforded a nearly colourless zone from which 5-*ethylchrysene*, plates, m. p. 113—114° (10 mg.) (from ethanol), was obtained (Found: C, 93·6; H, 6·2. $C_{20}H_{16}$ requires C, 93·7; H, 6·3%). The *s*-trinitrobenzene *complex* formed yellow needles, m. p. 145—146° (Found: N, 9·2. $C_{26}H_{19}O_6N_3$ requires N, 8·95%).

(*b*) 5-Acetylchrysene (50 mg.) was reduced by the Clemmensen method as described above for the 4-isomer. The product was chromatographed in light petroleum (b. p. 60—80°) on alumina and crystallised from ethanol, yielding plates (30 mg.), m. p. 113—114° alone or mixed with the product obtained as above. Identity was confirmed by comparison of the *s*-trinitrobenzene complexes.

2-*Ethylchrysene*.—2-Acetylchrysene was reduced in the manner described above for 4-acetylchrysene. The product was purified by chromatography in benzene solution on alumina. Crystallisation from ethanol afforded 2-ethylchrysene in needles, m. p. 124—125° (lit. 124—125°).

This work was carried out by the author as a member of staff of the Medical Research Council. He is indebted to Professor J. W. Cook, F.R.S., for his interest and encouragement. Microanalyses were by Mr. J. M. L. Cameron and Miss M. Christie.

UNIVERSITY OF GLASGOW. [*Received, July 1st,* 1953.]

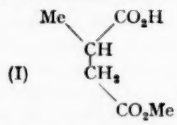
702. 1 : 2-*Dicarboxylic Acids. Part I. Positional Isomerides Derived from Methylsuccinic Acid; with a Note on the Rearrangement of Unsymmetrical Compounds of this Type.*

By J. E. H. Hancock and R. P. Linstead.

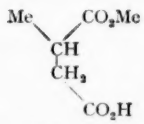
The two positionally isomeric half methyl esters (I and II) of methylsuccinic acid have been obtained in a pure crystalline state for the first time. Isomeride (I) was best prepared by hydrogenation of the corresponding half-ester of itaconic acid (IV); isomeride (II) was isolated by low-temperature crystallisation of the mixture obtained by esterification of methylsuccinic anhydride. These half-esters have been converted into the corresponding anilic esters which have been linked with the two anilic acids obtained from methylsuccinic anil. The structures of the various isomerides have been established and the work connected with that of previous investigators. Alkaline hydrolysis of the two anilic esters gives the same mixture of anilic acids and appears to proceed abnormally through intermediate formation of the anil. Electrolysis of the mixed half-esters gave a mixture of dimethyladipic esters from which *meso*-αα′-dimethyladipic acid was prepared.

This series of papers will be largely concerned with derivatives of acids of the succinic and maleic series. Apart from their intrinsic interest, for example their ring closure to heterocyclic compounds and their rearrangements, they are of particular value as intermediates for the synthesis of conjugated macrocycles.

The two half-esters of methylsuccinic acid were recently required as intermediates in anodic syntheses. There was no definite evidence in the literature that either had ever been obtained pure, and a similar obscurity surrounded some other related unsymmetrical derivatives. As this is the simplest acid which can provide positionally isomeric derivatives of the types exemplified by the half-esters (I) and (II), it was desirable to determine whether two such series of compounds could be prepared in a homogeneous state and with known structure. This has now been done.



(I)



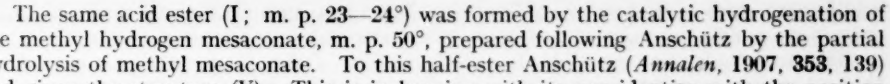
(II)

Previous preparations of the half-esters of methylsuccinic acid had yielded oily products, alike from the partial hydrolysis of diesters, partial esterification of the acid, and reaction of the anhydride with alcohols (Brühl and Braunschweig, *Ber.*, 1993, **26**, 337; Bone, Sudborough, and Sprankling, *J.*, 1904, **85**, 534). Half-esters prepared by these different methods had very similar physical properties, and, in the light of evidence presented later, there is no doubt that they were mixtures of positional isomers of types (I) and (II). A recent patent (U.S.P. 2,444,735) described the preparation of a half methyl ester by the interaction of methyl pyruvate and keten, followed by reduction of an intermediate β-lactone. Although this product was claimed to be the individual isomeride (II), it also was a liquid.

Our first experiments were on two processes which seemed likely to yield a homogeneous compound. In itaconic acid (III) the two carboxyl groups are attached to an unsaturated and a saturated carbon atom, respectively. This makes a well-established and decisive difference in their ease of esterification, and partial esterification following Anschütz and Drugman (*Ber.*, 1897, **30**, 2649, 2652) gave a homogeneous monomethyl ester to which the structure (IV) can be given with confidence. Catalytic hydrogenation of this gave a single methyl hydrogen methylsuccinate of m. p. 23—24°, which is assigned the methyl β-carboxybutyrate structure (I).*

* Since the completion of the present work, B. R. Baker, Schaub, and Williams (*J. Org. Chem.*, 1952, **17**, 116) have described the preparation of a methyl hydrogen methylsuccinate by the same route and have proved it to have the structure (I) by an independent method. Their material was obtained as an oil but there can be no doubt that it was substantially identical with ours. Other points raised by the work of Baker *et al.* are dealt with later.

The same acid ester (I; m. p. 23—24°) was formed by the catalytic hydrogenation of the methyl hydrogen mesaconate, m. p. 50°, prepared following Anschütz by the partial hydrolysis of methyl mesaconate. To this half-ester Anschütz (*Annalen*, **1907**, **353**, 139) had given the structure (V). This is in keeping with its non-identity with the position



(III) (IV) (V)

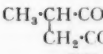
isomer prepared by Cloez (*Bull. Soc. chim.*, 1890, **3**, 598), and with Cocker and Fateen's recent proof of the structure of the ethyl hydrogen mesaconate prepared in a similar way (*J.*, 1951, 2630). The assignment of structure (I) to the half-ester of m. p. 23—24° agrees with these results.

The formation of half methyl esters from methylsuccinic anhydride was next examined. The product was a liquid mixture of isomers. When kept at low temperature it deposited a solid which after crystallisation from ether–light petroleum at −70° gave prisms of a second methyl hydrogen methylsuccinate, m. p. 42—43°. The same compound was obtained by partial esterification of methylsuccinic acid. The considerable practical difficulties in the isolation of this solid are described in the experimental section.

It was necessary to establish that the new solid was a definite position isomer and not a crystalline modification of the half-ester of m. p. 24°. For this purpose the two half-esters were converted into the ester anilides which were independently prepared from the anilic acid. Morrell (*J.*, 1914, **105**, 2698) had reported two anilic acids, m. p. 159° and 123°, and previous workers (Arppe and Biffi, *Annalen*, 1854, **90**, 141; Anschütz, *ibid.*, 1888, **246**, 122; **248**, 273; Bone and Sprankling, *J.*, 1899, **75**, 859) had obtained one isomer, m. p. 148° (Anschütz, 143°). In our experiments the anil of methylsuccinic acid was hydrolysed with alkali, and the anilic acids liberated by fractional acidification and purified by crystallisation. Two isomeric anilic acids were obtained, one homogeneous of m. p. 149—150° and one of m. p. 118°, which subsequent work showed to be the nearly pure second form. The higher-melting isomer appears to exist in two crystalline modifications as is shown by Cocker and Fateen's work (*loc. cit.*). Treatment of the two anilic acids with diazomethane gave the corresponding anilic esters; the acid of m. p. 149° giving a homogeneous ester, m. p. 80°, and the acid of m. p. 118° a slightly impure ester which on crystallisation readily gave a pure compound, m. p. 85°. The m. p.–composition curve of the two isomeric anilic esters showed a considerable depression, there being a single eutectic, m. p. 55°, containing 52% of the isomeride of m. p. 80° [methyl α-(phenylcarbamylmethyl)-propionate (VI; R = OMe, R′ = NHPh)].

The two half methyl esters, m. p.s 24° and 43°, were linked to these two anilic esters through the ester chlorides. It has recently been established that the preparation of ester chlorides from unsymmetrical half-esters of the succinic, glutaric, or phthalic series may involve rearrangement (Cason, *J. Amer. Chem. Soc.*, 1947, **69**, 1548, etc.; Salmon-Legagneur and Soudan, *Compt. rend.*, 1944, **218**, 681; Ställberg-Stenhagen, *J. Amer. Chem. Soc.*, 1947, **69**, 2568; Chase and Hey, *J.*, 1952, 553), but Ställberg-Stenhagen has shown that this can be avoided by the use of oxalyl chloride under mild conditions. Using the same precautions, we converted the half-ester of m. p. 43° into the anilic ester of m. p. 80° and the half-ester of m. p. 24° into the anilic ester of m. p. 85°. In this way the existence of two distinct isomeric series was confirmed and the structure of the various compounds established (see the Table).

Positional isomerides of methylsuccinic acid (VI).

 (VI)	R	OH	NHPh	NHPh	NMePh	NMePh	OMe	OMe	OH
	R′	OMe	OMe	OH	OMe	OH	OH	NHPh	NHPh
	M. p.	24°	85°	118° *	101°	149°	43°	80°	149°

* Not quite homogeneous.

The two isomeric anilic esters did not hydrolyse normally with cold aqueous alkali. Each gave a gum which subsequently solidified and then passed into solution; subsequent

acidification gave a ***mixture*** of anilic acids. From the mixture derived from the anilic ester of m. p. 85°, the anilic acid of m. p. 149°, belonging to the other series, was isolated.

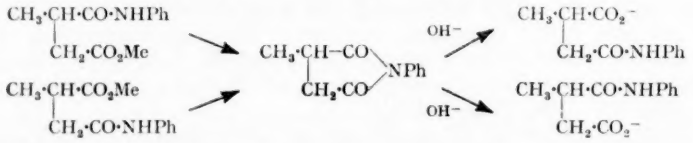
The *N*-methylanilic ester (VI; R = NMePh, R′ = OMe), m. p. 101°, was made from the half-ester of m. p. 24° through the ester chloride in the usual way. On hydrolysis with alkali it gave a homogeneous *N*-methylanilic acid which regenerated the original *N*-methylanilic ester, m. p. 101°, with diazomethane. The isomeric *N*-methylanilic ester derived from the half-ester of m. p. 43° was not obtained crystalline.

Further reference can now be made to the work of Baker, Schaub, and Williams (*loc. cit.*). From the (liquid) half-ester (I) by the same method they also obtained the *N*-methylanilic ester (VI; R = NMePh, R′ = OMe) of m. p. 100—101°, clearly identical with ours. By hydrolysis of this with hot alkali they obtained the corresponding acid (VI; R = NMePh, R′ = OH) which melted at 161—161·5° when pure. Our *N*-methylanilic acid melted at 149°. It seems probable that this discrepancy is due to dimorphism which is also encountered with the anilic acid (VI; R = OH, R′ = NHPh). The alternative explanation that our material contained some rearranged product seems unlikely because (*a*) our method of hydrolysis was milder than that used by Baker *et al.*, and (*b*) our acid regenerated the parent methyl ester with diazomethane. The second *N*-methylanilic acid (VI; R = OH, R′ = NMePh) has been prepared by Baker *et al.*; it melts at 77—78°. The American workers made the interesting observation that this material was rearranged to the high-melting isomer (at least partially) at 100°.

The Rearrangement of Unsymmetrical Derivatives of Succinic and Similar Acids.

It seems appropriate to make some comments on the mechanism of rearrangement of these unsymmetrical derivatives. These will be restricted to three examples: (i) our rearrangement of the anilic esters of methylsuccinic acid on alkaline hydrolysis; (ii) the thermal rearrangement of the *N*-methylanilide of methylsuccinic acid observed by Baker *et al.*; and (iii) the well-known rearrangement of the acid chlorides of half esters, recently reviewed in some detail by Chase and Hey (*loc. cit.*).

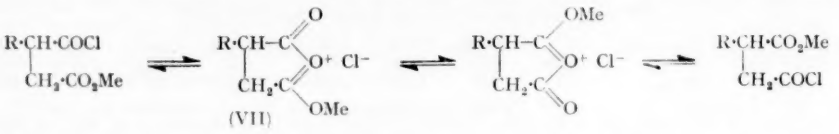
For reaction (i) the most probable mechanism is a preliminary elimination of methanol with the formation of the anil, followed by the fission of this by hydroxide ion, which is known to occur in both directions giving the two anilic acid ions :



This is supported by the absence of rearrangement in the hydrolysis of the *N*-methylanilic ester which cannot form the anil.

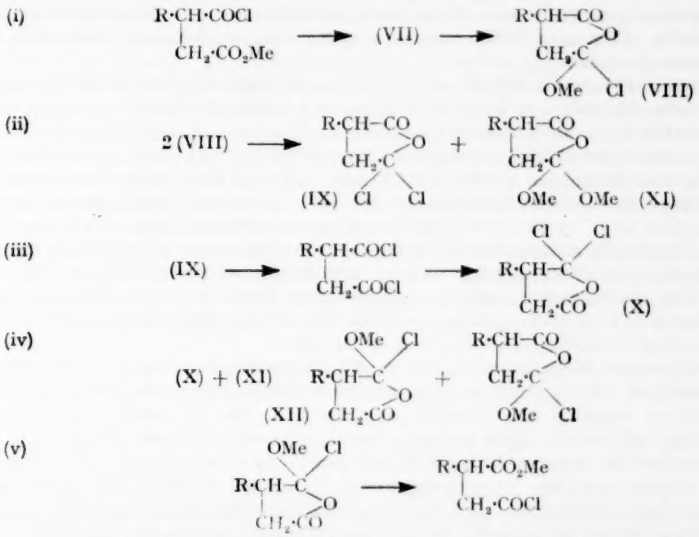
Reaction (ii) reasonably goes through anhydride which is subsequently split by methylaniline in both directions.

For reaction (iii) Chase and Hey mention as alternative intermediates the anhydride, an oxonium salt (VII), or an alkoxychlorolactone (VIII). It is debatable however, whether the last two are in fact alternatives. It seems plausible that the oxonium salt might well function as an intermediate in the formation of the lactone and that they are different stages in the same process. The crucial stage of the rearrangement is, however, the migration of the alkyl residue. One possibility is that this occurs in the cation of the oxonium salt :



This bears a resemblance to trans-esterification but involves an *O*-alkyl fission. A further possibility which does not appear to have previously been considered is that the alkoxy-

chlorolactone (VIII) disproportionates. The cyclic dichloride so formed (IX) undergoes a migration of chlorine; the new dichloride (X) then combines with a dimethoxy-compound (for example XI) by the reverse of the disproportionation; the isomeric alkoxychlorolactone (XII) is formed and this can tautomerise to the open-chain ester chloride with a structure isomeric with that of the starting material. The dimethoxy-compound involved in the reverse of the disproportionation can presumably have the open-chain or either of the two cyclic structures. The essential feature of this proposal is that it is a chlorine and not an alkoxy-group which migrates in the crucial stage.



It is possible to write a similar reaction scheme involving disproportionation of open-chain compounds but it would seem that the rearrangements are particularly easy among derivatives of acids which form heterocycles readily and reversibly : hence it is probable that the latter intervene, as has been generally thought.

The rearrangement may not necessarily involve the preformed half-ester half-chloride. It may occur during the reaction of the acid ester with the attacking reagent, such as thionyl chloride. Various special mechanisms involving the reagent then become possible.

Electrolyses. Preliminary experiments were carried out on the anodic coupling of the mixture of acid esters obtained by the action of methanol on methylsuccinic anhydride. This is rich in the isomer (II) of m. p. 43°. It was to be expected that in any case normal coupling of the Kolbe type would largely, if not exclusively, occur with this form and would be inhibited in the positional isomer because of the methyl group α- to carboxyl. Anodic coupling was carried out in methanol, by use of Linstead and Weedon's general technique (*J.*, 1950, 3326, etc). It gave a dimethyladipic ester fraction which on hydrolysis yielded some *meso*-αα'-dimethyladipic acid. This corresponds with the expected Kolbe coupling of the acid ester of m. p. 43°.

Experimental

Methylsuccinic anhydride was best prepared from the acid (*Org. Synth.*, **26**, 54) by Berner and Leonardsen's method (*Annalen*, 1939, **538**, 1). The yield of material, m. p. 33°, was 87%. Citraconic anhydride was hydrogenated extremely slowly over palladised barium sulphate in acetic acid or over Raney nickel in dioxan at 100°/100 atm.; this gave a 23% yield of the anhydride, m. p. 33°.

Methyl Hydrogen Methylsuccinate, m. p. 24° (*Methyl* β-*Carboxybutyrate*) (I).—(*a*) Methyl hydrogen itaconate (IV; Anschütz and Drugman, *loc. cit.*) formed long needles, m. p. 70° (lit., 67°) after repeated crystallisation from chloroform–light petroleum (Found : C, 50·3;

H, 5·8. Calc. for $C_6H_8O_4$: C, 50·0; H, 5·6%). It could also be purified, although slowly, by sublimation (Found: C, 49·9; H, 5·6%). Material prepared from itaconic anhydride and methanol was less easily obtained pure (m. p. 67—71°).

Methyl hydrogen itaconate (13·3 g.) in methanol (130 c.c.) was hydrogenated over Adams's catalyst (0·94 g.). The oily product, freed from catalyst and solvent, was seeded and set aside for several days in a vacuum desiccator at 0°. The crystallised material was filtered off at 0°, pressed on a pre-cooled porous tile, and finally recrystallised from ether–light petroleum at −80°. This gave crystals (4·63 g.), m. p. 15—22°, yielding after 3 similar recrystallisations, pure methyl β-carboxybutyrate (I), m. p. 23—24·2°. The oily filtrate, which contained unsaturated material, yielded more of the same product after rehydrogenation under 5 atmospheres pressure. The m. p. of the ester of m. p. 24° was somewhat depressed after distillation at 90°/0·8 mm. (bath-temp.).

(*b*) Dimethyl mesaconate was made by esterification following Stosius and Phillips's method (*Monatsh.*, 1924, **45**, 467). A solution of potassium hydroxide (8·9 g.) in methanol (150 c.c.) at 0° was treated slowly with dimethyl mesaconate (25 g.) in methanol (70 c.c.). After 52·5 hr., the product was separated by conventional procedures into acid and neutral fractions. The acid fraction after distillation at 149—157°/21 mm. (14·8 g.; 76%, with allowance for recovered diester) solidified to a mass of needles, m. p. 40—48°. Repeated crystallisation from petroleum gave a constant m. p. of 48—50·5°, unchanged by regeneration from the sodium salt. This pure methyl hydrogen mesaconate (V) (8·1 g.) was hydrogenated over Adams's catalyst in dry methyl acetate, first at atmospheric pressure and finally, after the addition of fresh catalyst, at 5 atm. The oily product was left to crystallise at 0° for several days in the presence of a seed of the half-ester of m. p. 24°. Seven crystallisations of the solid product from ether–petroleum gave pure methyl β-carboxybutyrate (I), m. p. 23—24°.

Methyl Hydrogen Methylsuccinate, m. p. 43° (*β-Carbomethoxybutyric Acid*) (II).—Methylsuccinic anhydride (32·2 g.) was heated under reflux with anhydrous methanol (11·5 c.c.) for 35 min. Next morning the product was distilled, 33·1 g. (80%) distilling at 93·5—94·7°/0·5 mm., n_D^{24} 1·4307. This material deposited much solid when kept at 0° for several days but the product very easily liquefied and gave only a few crystals when filtered through pre-cooled apparatus at 0°. It was accordingly dissolved in ether–light petroleum, and the temperature slowly lowered to −70°, a slight turbidity being maintained. The crystals which separated were filtered off at −80°, pressed on pre-cooled porous tile, and kept in a vacuum desiccator for several days at 0°. 1·53 g. of material melting at about 36—42° were obtained. Three repetitions of this process gave prisms of the pure β-carbomethoxybutyric acid (II), m. p. 42·5—43·5°. The analytical sample was dried at room temp. and 10^{-5} mm. (Found: C, 49·4; H, 7·1. $C_6H_{10}O_4$ requires C, 49·3; H, 6·9%) The *half-ester* was nearly unchanged after sublimation at 70°/10^{-2} mm. (bath temp.) (m. p. 41·5—43·5°).

Partial esterification of methylsuccinic acid with methanol (Fischer–Speier conditions; room temperature) gave, in addition to dimethyl ester, an acid ester fraction which failed to solidify when seeded with the half-ester of m. p. 24°. By the techniques described above, material, m. p. 38—41°, was obtained which was substantially the same as that made from the anhydride. Partial hydrolysis of the dimethyl ester with cold methanolic potash yielded an acid ester fraction in 65% yield, having b. p. 85·5°/0·3 mm., n_D^{24} 1·4305 (Found: equiv., 145·9. Calc., 146·1). This partially crystallised when seeded at 0° with the half-ester of m. p. 43° but not with the isomeride, m. p. 24°.

Anilic Acids and Esters from Methylsuccinic Anil.—The anil was prepared from the acid and aniline by Morrell's method (*loc. cit.*). The yield of the distilled product was 96%; the m. p. after three crystallisations from water was 105°. The anil sublimed slowly at 100° under atmospheric pressure.

The anil (7·1 g.) was treated for 30 min. with 2N-sodium hydroxide (22·5 c.c.). The clear solution was acidified with 2N-hydrochloric acid, added dropwise with mechanical stirring. Solid was collected at intervals, washed with water, dried (NaOH) at 0·1 mm., and weighed. In this way a total yield of 95% of anilic acid was obtained. The first crop (about 50%) melted at 143—145° and after two crystallisations from ethyl acetate gave α-(phenylcarbamylmethyl)-propionic acid (VI; R = OH, R′ = NHPh), m. p. 148·5—150·5°. After seven further crops of mixed anilic acids had separated, the residual solution was acidified with concentrated hydrochloric acid and cooled in ice–salt. The final product so precipitated (120 mg.; m. p. 111—112·5°) had m. p. 117·5—118° after three crystallisations from chloroform and was almost pure β-phenylcarbamylbutyric acid (VI; R = NHPh, R′ = OH).

The two anilic acids were esterified with ethereal diazomethane. The isomeride of m. p.

149° gave *methyl* α-(*phenylcarbamylmethyl*)*propionate* (VI; R = OMe, R′ = NHPh), m. p. 79·4—80° (from petroleum containing a little benzene) (Found: C, 65·2; H, 7·0; N, 6·3. $C_{12}H_{15}O_3N$ requires C, 65·1; H, 6·8; N, 6·3%). The ester from the anilic acid of m. p. 118°, twice crystallised from petroleum, melted at 82·5—84°. A mixture with the anilic ester, m. p. 85°, prepared as described below, melted at 84°. The substance was therefore nearly pure methyl β-phenylcarbamylbutyrate (VI; R = NHPh, R′ = OMe).

Anilic Esters from Acid Esters of Methylsuccinic Acid.—Methyl β-carboxybutyrate (I; m. p. 24°; 655 mg., from methyl hydrogen mesaconate) in dry benzene (1 g.) and oxalyl chloride (657 mg.) were warmed at 30—40° for 3 hr., and the solvent evaporated at 40°/12 mm. The product was taken up in dry benzene and again evaporated, and this operation was repeated twice. The residue was dissolved in dry ether (4 c.c.) and carefully treated at 0° with aniline (1·2 c.c.) in the same solvent. The neutral product, isolated in the usual manner (782 mg., 79%), was pure *methyl* β-*phenylcarbamylbutyrate* (VI; R = NHPh, R′ = OMe), m. p. 84—85°. A similar preparation from methyl β-carboxybutyrate, m. p. 24° [prepared from methyl hydrogen itaconate (IV)] and three crystallisations of the anilic ester from petroleum yielded fine needles, m. p. 84—85° (Found: C, 65·2; H, 7·0; N, 6·55. $C_{12}H_{15}O_3N$ requires C, 65·1; H, 6·8; N, 6·3%). The correct values for carbon and hydrogen were obtained only by combustion of the compound mixed with potassium dichromate. There was no depression in melting point when the two preparations described above were mixed.

The isomeric half-ester (II), m. p. 43°, was similarly treated with oxalyl chloride, followed by aniline. The product (81%) was methyl α-(phenylcarbamylmethyl)propionate (VI; R = OMe, R′ = NHPh), m. p. 79—80·5° not depressed on admixture with a sample prepared by esterification of the anilic acid, m. p. 149°, but greatly depressed by the isomeric anilic ester, m. p. 85°.

A melting point–composition curve was determined for mixtures of the two anilic esters. Such mixtures began to soften at 50—60°; the temperatures given below are those when a homogeneous liquid was formed:

% of (VI; R = OMe, R′ = NHPh) ...	0	10	21	32	40	50	59	70	79	90	100
M. p., °C	85	82	78·5	72	64	57	61·5	68	73	78	80

The eutectic contains 52% of (VI; R = OMe, R′ = NHPh) and is at 54·5°.

Mixtures of the isomeric half methyl esters of methylsuccinic acid could be roughly analysed by conversion through the ester chloride into the anilic ester, followed by determination of m. p. and mixed m. p.s. The mixed anilic ester first separated as a gum which was difficult to manipulate; and this lessened the quantitative significance of the results. The indications were that the mixed half-ester obtained by esterifying methylsuccinic anhydride contained about two-thirds of the isomeride (I); while in that from partial hydrolysis of the diester the compound (II) preponderated.

Alkaline Hydrolysis of Anilic Esters.—Methyl β-phenylcarbamylbutyrate (VI; R = NHPh, R′ = OMe) (157 mg.), m. p. 85°, was treated with N-potassium hydroxide (1 c.c.); a gum separated which rapidly solidified. On the addition of alcohol (5 c.c.), the mixture became homogeneous. After 12 days at room temperature the solvent was removed in a vacuum-desiccator, the gum was dissolved in a little water, and the product acidified with N-hydrochloric acid (2·5 c.c.). After a night at 0° the precipitated anilic acid was filtered off and washed with water at 0°. The undissolved portion (98 mg., 67%) melted at 134—137°; the filtrate slowly deposited a solid, m. p. 117—120° (20 mg., 14%). The solid of m. p. 134—137° after four crystallisations from ethyl acetate melted at 147—148°, and at 148—148·5° in admixture with the anilic acid of m. p. 149° (VI; R = OH, R′ = NHPh). The low-melting fractions were mixtures from which the isomeric anilic acid (VI; R = NHPh, R′ = OH), m. p. 117·5—118°, was obtained nearly pure by crystallisation from chloroform (Found: C, 63·0; H, 6·3. Calc. for $C_{11}H_{13}O_3N$: C, 63·75; H, 6·3%).

Methyl α-(phenylcarbamylmethyl)propionate (VI; R = OMe, R′ = NHPh), m. p. 80°, was hydrolysed similarly. It gave in 74% yield a similar mixture, m. p. 129—136°, of anilic acids. The pure anilic acid, m. p. 149°, was quite unaffected by treatment with alkali under the conditions of hydrolysis.

Methyl β-carboxybutyrate (I; m. p. 24°) was converted into the corresponding *N*-methylanilic ester by successive treatments with oxalyl chloride and *N*-methylaniline, following the procedure given above for the corresponding anilide. The reaction product melted at 97—100·5° and gave the homogeneous *methyl* β-*N-methylphenylcarbamylbutyrate* (VI; R = NMePh, R′ = OMe), m. p. 100·5—101°, constant after one crystallisation from ethyl acetate–petroleum (Found: C, 67·3; H, 7·4; N, 6·0. $C_{13}H_{17}O_3N$ requires C, 66·4; H, 7·3; N, 6·0%).

The *N*-methylanilic ester was hydrolysed with alkali by the method described for the anilic esters. The crude acid, isolated in almost quantitative yield, after one crystallisation from ethyl acetate gave β-*N*-*methylphenylcarbamylbutyric acid* (VI; R = NMePh, R′ = OH), as prisms, m. p. 148·5—149·5° (Found : C, 65·8; H, 7·0; N, 7·1. $C_{12}H_{15}O_3N$ requires C, 65·1; H, 6·8; N, 6·3%). Esterification with diazomethane re-formed the original *N*-methylanilic ester; m. p. 99—100° (crude), 99—100·5° after one crystallisation, mixed m. p. the same.

Electrolysis of Mixed Half-esters of Methylsuccinic Acid.—The general technique described by Linstead and Weedon (*loc. cit.*) was followed. The mixed half-ester, obtained by esterifying methylsuccinic anhydride (10·7 g.), in anhydrous methanol (25 c.c.) containing 0·02 equiv. of sodium was electrolysed by a current of 1·5 A at 110 V between smooth platinum electrodes. After 107 min. the mixture became alkaline, this corresponding to a 36% excess of current over the theoretical. The product was acidified with a few drops of acetic acid and freed from solvent. On distillation 2·24 g. of a neutral oil were obtained, b. p. 112—116°/13 mm., $n_D^{22\cdot5}$ 1·4295; corresponding to a 30% yield of dimethyladipic ester. This fraction was hydrolysed with boiling hydrochloric acid (1 : 1). The product was a gum which after some months deposited a solid; this was triturated with benzene and filtered off; it had m. p. 128—139°. The yield of gummy acid was nearly theoretical but that of solid was only 7%. After three crystallisations from hydrochloric acid (1 : 1) the solid gave prisms of *meso*-αα′-dimethyladipic acid, m. p. 141—142° alone or in admixture with an authentic specimen (Noyes and Kyriakides, *J. Amer. Chem. Soc.*, 1910, **32**, 1057).

Analyses were carried out in the microanalytical laboratory of this Department (Mr. Oliver).

We thank the Department of Scientific and Industrial Research for a Maintenance Grant (to J. E. H. H.) and Dr. E. A. Braude for helpful discussion.

Department of Organic Chemistry, Imperial College of Science and Technology, South Kensington, S.W.7. [*Received, July 2nd*, 1953.]

---

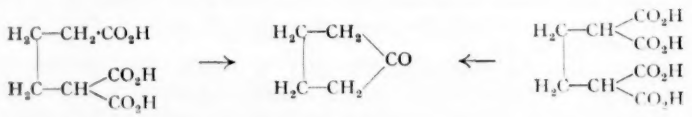
703. *The Direct Formation of* cyclo*Pentanones by the Action of Mineral Acids on Carboxy-adipic Acids and Related Compounds.*

By L. Crombie, J. E. H. Hancock, and R. P. Linstead.

α-Carboxy- and α-cyano-adipic acids are found to yield *cyclo*pentanones when heated with hydrobromic acid : the reaction is largely specific for the formation of a five-membered ring. Its structural requirements are examined and a mechanism suggested. This leads to the rationalisation of certain previously unexplained observations in the literature.

Some features of interest are summarised concerning the preparation of compounds required in the investigation.

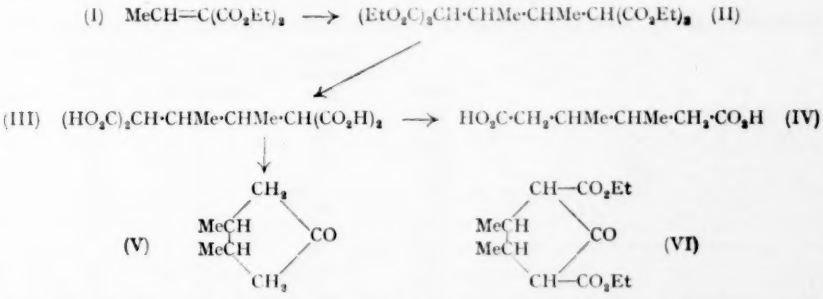
The formation of *cyclo*pentanone and its derivatives from the corresponding adipic acids or esters, by such methods as those of Blanc and of Dieckmann, are among the classical reactions of organic chemistry. We now find that mono- and di-α-carboxyadipic acids give substantial yields of *cyclo*pentanone when boiled with mineral acid.



This reaction has been generalised and its structural requirements and a possible mechanism have been established. It occurs under very much milder conditions than those prevailing in the usual pyrolytic formation of cyclic ketones from adipic acids.

The occurrence of the reaction was first established during the preparation of βγ-dimethyladipic acid (IV). The synthetical route was the bimolecular reduction of ethylidenemalonic ester (I) with aluminium amalgam and moist ether to the tetracarboxylic

ester (II) (Vogel, *J.*, 1927, 1985; Ställberg-Stenhagen, *Arkiv Kemi*, 1951, **3**, 256), followed by hydrolysis to the tetra-acid (III) and decarboxylation to (IV):

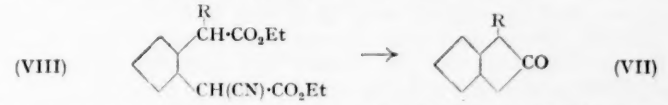


The last two stages were carried out by the usual procedure with boiling concentrated hydrochloric acid. This gave, however, not only the acid (IV) but a 30% yield of the corresponding 3 : 4-dimethyl*cyclo*pentanone (V). Both these were mixtures of the two possible stereoisomerides. The acid yielded the pure *meso*-isomeride after many crystallisations; the ketone (which was characterised by the preparation of its 2 : 4-dinitrophenylhydrazone, oxime, semicarbazone, and dibenzylidene derivative) is estimated from thermal analysis to contain about 80% of the *trans*-form.

A plausible explanation for the unexpected appearance of the cyclic ketone was that it had come from the hydrolysis of cyclic material, such as the keto-diester (VI), already formed during the bimolecular reduction. Indeed, when this reaction was carried out by the usual technique, so that the ether used as reaction medium boiled, the tetra-ester fraction gave a pronounced ferric chloride colour. However, this explanation was insufficient, for, when the reduction was conducted by two successive treatments at 0—5°, a pure tetra-ester was obtained. This gave no ferric chloride colour but, when boiled with hydrochloric acid, yielded no less than 45% of the cyclic ketone (V) together with 52% of the acid (IV).

The hydrolysis of cyano- and carbethoxy-derivatives of adipic esters has been for years a standard method of obtaining the corresponding dicarboxylic acids, and the formation of volatile ketones in this way is a factor leading to appreciable losses in yield. The Table on page 3498 shows that when no cyclisation occurs the yield of dicarboxylic acid is nearly quantitative.

A few indications of this type of cyclisation can be found in the literature. Barrett and Linstead (*J.*, 1935, 436) observed the formation of small amounts of *cis*-*bicyclo*[3 : 3 : 0]-octan-3-one (VII; R = H) by the hydrolysis of (VIII; R = H).



Koelsch and Stratton (*J. Amer. Chem. Soc.*, 1944, **66**, 1881) and Birch and Johnson (*J.*, 1951, 1493) have also obtained cyclic ketonic products from similar series of reactions which involved both reductions with aluminium amalgam and acid hydrolysis, but in no case was it definitely established at which stage the cyclisation occurred. In the light of the new results there is little doubt that the formation of the *bicyclo*octanone occurs during the hydrolytic stage, and this would agree with the recent work of Šorm, Šormova, and Sedivy on the corresponding methylated compounds (VII and VIII; R = Me) (*Coll. Czech. Chem. Comm.*, 1947, **12**, 554).

We have investigated the effect of structural variation and of experimental procedure on the yield of ketone. The highest yields (up to nearly 80%) are given when aqueous hydrobromic acid is used in the hydrolysis. The use of toluene-*p*-sulphonic acid in benzene or of trifluoroacetic anhydride gave no detectable ketone.

For the examination of structural variations twenty poly-acids or -esters were used, with the results summarised in the Table.

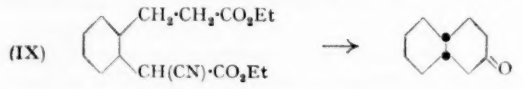
Products resulting from the treatment of polycarboxylic compounds with mineral acids.

	Acid [f]	Time for homogeneity, min.	Yield of ketone, % [*]	Yield of diacid, %	Material accounted for, %
$CHEt(CO_2Et)_2$	HBr	—	0	—	—
$(EtO_2C)_2CH{\cdot}[CH_2]_3{\cdot}CO_2Et$	HCl	23	10	83	93
$(EtO_2C)_2CH{\cdot}[CH_2]_3{\cdot}CO_2Et$	HBr	3	48	50	98
$(HO_2C)_2CH{\cdot}[CH_2]_3{\cdot}CO_2H$	HBr	1	42	50	92
$(EtO_2C)_2CH{\cdot}[CH_2]_2{\cdot}CH(CO_2Et)_2$	HCl	1·25 hr.	27	67	94
$(EtO_2C)_2CH{\cdot}[CH_2]_2{\cdot}CH(CO_2Et)_2$	HBr	18	78	21	99
$(HO_2C)_2CH{\cdot}[CH_2]_2{\cdot}CH(CO_2H)_2$	HBr	4	79	19	98
$(EtO_2C)_2CMe{\cdot}[CH_2]_2{\cdot}CMe(CO_2Et)_2$ [a]	HBr	—	—	—	—
$(HO_2C)_2CMe{\cdot}CH_2]_2{\cdot}CMe(CO_2H)_2$	HBr	8 hr.	0	90	90
$(MeO_2C)_2CH{\cdot}[CHMe]_2{\cdot}CH(CO_2Me)_2$ [b]	HCl	1·5 hr.	21	76	97
$(EtO_2C)_2CH{\cdot}[CHMe]_2{\cdot}CH(CO_2Et)_2$ [c]	HCl	7·75 hr.	45	52	97
$(EtO_2C)_2CH{\cdot}[CHMe]_2{\cdot}CH(CO_2Et)_2$ [c]	HBr	—	73	15	98
$MeO_2C{\cdot}[CH_2]_4{\cdot}CO_2Me$	HCl	2	0	100	100
$EtO_2C{\cdot}[CH_2]_4{\cdot}CO_2Et$	HBr	—	0	100	100
$HO_2C{\cdot}CH_2{\cdot}[CHMe]_2{\cdot}CH_2{\cdot}CO_2H$ [d]	HCl	—	0	100	100
$(EtO_2C)_2CH{\cdot}[CH_2]_3{\cdot}CH(CO_2Et)_2$	HBr	22	0	96	96
$(HO_2C)_2CH{\cdot}[CH_2]_3{\cdot}CH(CO_2H)_2$	HBr	—	0	99	99
$(EtO_2C)_2CH{\cdot}CH_2{\cdot}CH(CO_2Et)_2$	HBr	15	0	100	100
$(EtO_2C)_2CH{\cdot}[CH_2]_5{\cdot}CH(CO_2Et)_2$	HBr	25	0	100	100
$(EtO_2C)_2CH{\cdot}[CH_2]_6{\cdot}CH(CO_2Et)_2$	HBr	25	0	100	100
$EtO_2C{\cdot}CH(CN){\cdot}[CH_2]_3{\cdot}CO_2Et$	HBr	—	35	69 [e]	—
$EtO_2C{\cdot}CH(CN){\cdot}[CH_2]_4{\cdot}CO_2Et$	HBr	—	0	99 [e]	—
(VIII; R = H)	HBr	2	20	—	—

[*] As 2 : 4-dinitrophenylhydrazone.

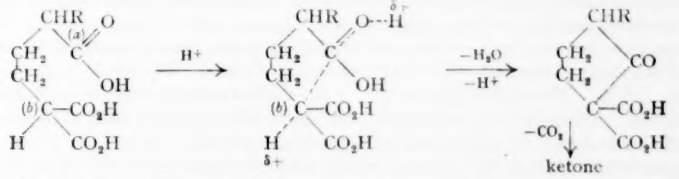
[a] Discontinued as the precipitation of tetra-acid caused experimental difficulty : no ketone was detected. [b] *meso*-. The 2 : 4-dinitrophenylhydrazone had m. p. 148—148·5° and the *meso*-dimethyladipic acid, m. p. 132—133°. [c] Mixture of stereoisomers obtained from the low-temperature bimolecular reduction. [d] This was not carried out in the special apparatus, but a 12 hr. reaction period yielded no ketone. [e] Adipic acid contaminated with ammonium bromide. [f] HBr indicates constant-boiling acid and HCl a 1 : 1-mixture of acid and water.

The main conclusions which we draw are as follows: (1) Tri- and tetra-carboxylic acids (and esters) of the adipic series all give the corresponding *cyclo*pentanones when boiled with aqueous hydrogen bromide. (2) The species responsible for cyclisation are the acids not the esters; no ketone can be detected when tetramethyl butane-1 : 1 : 4 : 4-tetracarboxylate is boiled with hydrogen bromide until the mixture becomes homogeneous; on the other hand the formation of ketone from the corresponding acid is immediate. (3) Acids of the adipic series containing no additional carboxyl or similar groups yield no *cyclo*pentanones under these conditions. If one additional carboxyl or cyano-group is present the yield of *cyclo*pentanone is about 40%. If two such groups are present the yield rises to about 70%. The highest yield observed was that of *cyclo*pentanone itself from butane-1 : 1 : 4 : 4-tetracarboxylic acid (79%). (4) The formation of cyclic ketones is prevented if both α-carbon atoms are alkylated. (5) *cyclo*Hexanones are not formed from carboxyl, carbalkoxyl, or cyano-derivatives of pimelic acid, which give quantitative yields of pimelic acid when boiled with hydrobromic or hydrochloric acids. The single known exception to this rule is provided by the conversion of (IX) into the *cis*-β-decalone (X) by boiling hydrochloric acid (Barrett,



Cook, and Linstead, *J.*, **1935**, 1065). The yield is however quite small. Steric conditions may be presumed to be unusually favourable for cyclisation in this case. (6) It is not surprising that no *cyclo*butanone, *cyclo*heptanone, or *cyclo*octanone is formed by the treatment of the appropriate tetracarboxylic ester with boiling hydrogen bromide. (7) Dipropyl ketone is not formed by an analogous intermolecular reaction from ethylmalonic acid. In another case diethyl malonate gave no acetone.

This acid-catalysed cyclisation of carboxy-adipic acids is assigned the following mechanism :



If R = CO_2H, there will be an additional decarboxylation in the final stage. Attack is initiated by a proton at the carbonyl group of one carboxyl (*a*); a cyclic transition state is formed in which the bond (*b*) attaching the hydrogen to the malonic acid residue is weakened; the cyclisation is completed by the elimination of water from the potential carbonyl, formation of a carbon–carbon bond, and elimination of the " malonic " hydrogen. Decarboxylation completes the reaction. This mechanism explains why no cyclisation of αα′-dimethyl-acids is possible and why at least one end of the chain must carry two activating groups. We attribute the increase in yield from the cyclisation of the tetracarboxylic acids to a statistical effect.

The clear-cut distinction between the adipic and pimelic series is surprising, for they are usually very similar in their capacity for cyclisation. The difference is attributed to the fact that ketonisation always competes with direct decarboxylation. Unless the system is very favourable for the formation of the cyclic intermediate (which is true for the carboxy-derivatives of adipic acids) then the malonic residues are decarboxylated, after which no cyclisation is possible.

Preparation and Purification of Materials.—It was clearly essential that the materials used in this work should be free from alicyclic products. The methods are described in the experimental section. A few incidental features of interest are summarised below.

(a) *Butane*-**1** : **1** : **4** : **4**-*tetracarboxylic ester.* This intermediate was used by Perkin in some classical syntheses of alicyclic compounds. His methods (*J.*, 1885, **47**, 807; 1887, **51**, 19; 1894, **65**, 578; 1895, **67**, 108; *Ber.*, 1886, **19**, 2038) have been improved by Noyes and Kyriakides (*J. Amer. Chem. Soc.*, 1910, **32**, 1057), who allowed ethyl magnesiomalonate to react with ethylene dibromide. The product, however, contains *cyclo*hexane-**1** : **1** : **4** : **4**-tetracarboxylic ester (Meincke, Cox, and McElvain, *ibid.*, 1935, **57**, 1133; Feofilaktov and Ivanov, *J. Gen. Chem. U.S.S.R.*, 1935, **5**, 1558), and enolic *cyclo*pentanone-carboxylic esters are also present. By employing a large excess of magnesiomalonate under controlled conditions, we have obtained tetraethyl butanetetracarboxylate for the first time as a crystalline solid, m. p. 17°. There is no doubt as to its homogeneity. The melting point is unchanged by regeneration from the sodio-compound; the ester yields an αα′-dimethyl derivative, and gives pure adipic acid on acid hydrolysis.

(b) *Butane*-**1** : **1** : **4**-*tricarboxylic ester.* This was prepared by treatment of diethyl adipate with dimethyl oxalate (Wislicenus and Schwanhäusser, *Annalen*, 1897, **297**, 111) and pyrolysis of the product. Another route was also employed—condensation of ethyl γ-bromobutyrate with sodiomalonic ester (cf. Montemartini, *Gazzetta*, 1896, **26**, II, 261; Boorman, Linstead, and Rydon, *J.*, 1933, 568). The bromo-ester was prepared in 82% yield by treatment of γ-butyrolactone with ethanolic hydrogen bromide at 0°; this is more convenient than previously described methods.

(c) **1**-*Cyanobutane*-**1** : **4**-*dicarboxylic ester and* **1**-*cyanopentane*-**1** : **5**-*dicarboxylic ester.* These were prepared by condensation of ethyl sodiocyanoacetate with the appropriate bromo-ester. Ethyl δ-bromovalerate was conveniently made from the corresponding δ-hydroxy-ester, formed by oxidising *cyclo*pentanone with persulphuric acid in ethanol (*cf.* Büchi and Jeger, *Helv. Chim. Acta*, 1949, **32**, 540).

(d) When diethyl ethylidenemalonate is reduced with aluminium amalgam, a low-boiling substance is formed as well as the bimolecular reduction product. Vogel (*loc. cit.*) assumed this to be diethyl malonate, but it is in fact diethyl ethylmalonate [$CHEt(CO_2Et)_2$].

Experimental

Analyses and light-absorption measurements were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mrs. A. I. Boston) laboratories of this Department.

Diethyl Ethylidenemalonate.—This was prepared according to Vogel's method (*loc. cit.*; cf. Ställberg-Stenhagen, *loc. cit.*), in a crude yield of 82%. It was fractionated through a Stedman column before use, and then had $n_D^{26\cdot5}$ 1·4385 (Found: C, 57·5; H, 7·65. Calc. for $C_9H_{14}O_4$: C, 58·05; H, 7·6%. Microhydrogenation: 1·00 double bond). Light absorption: $\lambda_{max.}$ 225 mμ, ε 5,600. Attempts to determine a saponification equivalent led to brown colours which masked the end-point (cf. Komnenos, *Annalen*, 1883, **218**, 162).

" Bimolecular " Reduction of Diethyl Ethylidenemalonate.—(a) *At reflux temperature.* Aluminium foil (90 g.), amalgamated according to Vogel's directions (*J.*, 1927, 594), was covered with ether, and diethyl ethylidenemalonate (240 g.) was added with stirring during 30 min. When the vigorous reaction had subsided, water was added (3 × 10 ml. and 1 × 30 ml.), and the product was stirred overnight. The sludge was filtered off and continuously extracted with ether.

After drying ($MgSO_4$), the combined ethereal solutions were evaporated and distilled. A low-boiling material (52·4 g.), b. p. 52—54°/0·5 mm., n_D^{20} 1·4161, was removed, and then tetraethyl 2 : 3-dimethylbutane-1 : 1 : 4 : 4-tetracarboxylate (196 g., 81%), n_D^{22} 1·4455—1·4462, distilled at *ca.* 146°/0·1 mm.

The low-boiling material was identified as diethyl ethylmalonate by further purification; it had n_D^{25} 1·4135 (Found: C, 57·25; H, 8·7. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·55%). On hydrolysis ethylmalonic acid, m. p. 112·5—114·5°, was isolated (lit., m. p. 112°), which decarboxylated at 160° to butyric acid. Vogel (*loc. cit.*) had assumed this by-product to be recovered diethyl malonate.

(b) *At low temperature.* Aluminium foil was prepared and amalgamated by Vogel's method except that the final washings with ethanol and ether were omitted. The amalgam (from 63 g. of Al) was covered with ether and stirred at 0°. Diethyl ethylidenemalonate (68·5 g.; $n_D^{26\cdot5}$ 1·4403) was added during 4 min. and the mixture stirred overnight at 0°. The solution was filtered, the solid washed with ether, and the united ethereal solutions dried and evaporated to yield a crude product (63·9 g.) which instantly decolorised permanganate. Reduction of this material was repeated with aluminium (49·5 g.) at 0°. After 35 min., water (5 ml.) was added and then further portions at hourly intervals (7 × 5 ml.). The temperature was kept below 10° and the mixture stirred overnight at 0° and worked up as described above. The crude product (49·6 g.) did not immediately reduce cold permanganate or give a colour with ferric chloride. Distillation gave diethyl ethylmalonate (16·8 g.), b. p. 48°/0·1 mm., $n_D^{21\cdot5}$ 1·4154, and tetraethyl 2 : 3-dimethylbutane-1 : 1 : 4 : 4-tetracarboxylate (31·5 g.), b. p. 70—80°/10^{-4} mm. (bath temp.), n_D^{20} 1·4452 (Found: C, 58·25; H, 8·25; OEt, 48·55. Calc. for $C_{18}H_{30}O_8$: C, 57·75; H, 8·1; OEt, 48·1%). Though it gave no ferric chloride colour, it still yielded a *cyclo*pentanone on treatment with acid (see Table).

Treatment of Tetraethyl 2 : 3-Dimethylbutane-1 : 1 : 4 : 4-tetracarboxylate with Acid.—The ester (196 g.) was refluxed with hydrochloric acid (165 ml.) and water (165 ml.), and the ethanol formed removed continuously through a small column during 8 hr. Finally it was refluxed overnight to complete decarboxylation. The liquid was then steam-distilled until the odour of ketone was no longer detectable (*ca.* 500 ml. of distillate). After decolorisation with charcoal, the solution of steam-involatile material was set aside at 0° for 2 days; a mixture of the stereoisomers of βγ-dimethyladipic acid (28 g., 31%; m. p. 124—130°) crystallised. The mother-liquors yielded a further 3·7 g. of crude material. Four recrystallisations of the main crop from ethyl acetate gave *meso*-βγ-dimethyladipic acid (14·2 g.), m. p. 131—133·3° (Ställberg-Stenhagen, *Arkiv Kemi*, 1951, **3**, 256, records m. p. 133—134°).

The steam-volatile ketonic material yielded 3 : 4-*dimethyl*cyclo*pentanone* 2 : 4-*dinitrophenylhydrazone* which, after five recrystallisations from ethanol, separated in yellow needles, m. p. 149·2—150° (Found: C, 54·0; H, 5·45; N, 19·15. $C_{13}H_{16}O_4N_4$ requires C, 53·45; H, 5·5; N, 19·5%). In a second experiment the crude derivative was chromatographed on alumina from benzene solution and ten fractions collected, the melting points of which lay between 140° and 147°.

The semicarbazone of the ketone (sodium acetate–semicarbazide hydrochloride method), after four crystallisations from methanol, had m. p. 205—207·5° (bath pre-heated to 196°). In a bath pre-heated to 209°, and with a temperature rise of 3·6°/min., the m. p. was 209·5—212°. Reference to a standard m. p. curve of mixtures of semicarbazones of *cis*- and *trans*-3 : 4-dimethyl*cyclo*pentanones indicated that the original ketone contained *ca.* 80% of *trans*-

isomer. It is interesting that Koelsch and Stratton (*J. Amer. Chem. Soc.*, 1944, **66**, 1882) obtained 3 : 4-diethyl*cyclo*pentanone, containing 90% of the *trans*-isomer, by acid hydrolysis of tetraethyl 2 : 3-diethylbutane-1 : 1 : 4 : 4-tetracarboxylate (obtained from a bimolecular reduction). Since the proportion of *meso*- and racemic forms in the starting material was not known, the possibility of preferential cyclisation of one of these cannot be discussed.

The *oxime* melted at 99·8—100·5° after 7 recrystallisations from aqueous ethanol (Found : N, 10·65. $C_7H_{13}ON$ requires N, 10·3%).

A *dibenzylidene* derivative had m. p. 113—114° (Found : C, 87·6; H, 7·05. $C_{21}H_{20}O$ requires C, 87·5; H, 7·0%). Light absorption ($CHCl_3$) : λ_{max} 349 mμ; ε 34,600 : $\lambda_{inf.}$ 353 mμ; ε 33,000. The 2 : 4-*dinitrophenylhydrazone* of the dibenzylidene derivative crystallised from ethanol in dark red needles, m. p. 220° (decomp.) (Found : C, 69·8; H, 5·0; N, 11·75. $C_{27}H_{24}O_4N_4$ requires C, 69·2; H, 5·15; N, 11·95%). Light absorption ($CHCl_3$) : $\lambda_{max.}$ 410, 600 mμ; ε 19,200, 28,200.

Tetraethyl meso-2 : 3-*Dimethylbutane*-1 : 1 : 4 : 4-*tetracarboxylate*.—*meso*-Acid (1·30 g.; m. p. 179°) was treated with ethereal diazomethane and yielded the *tetramethyl* ester. This crystallised from ethyl acetate–light petroleum (b. p. 60—80°) and then methanol in rhombohedra, m. p. 102·5—103·5° (Found: C, 52·9; H, 7·05; OMe, 39·3. $C_{14}H_{22}O_8$ requires C, 52·85; H, 6·95; OMe, 39·0%).

Tetramethyl Butane-1 : 1 : 4 : 4-*tetracarboxylate*.—Condensation of ethylene dibromide (slightly more than 1 mol.) with ethyl magnesiomalonate (2 mol.) gave, in a number of experiments, the required product contaminated with tetraethyl *cyclo*hexane-1 : 1 : 4 : 4-tetracarboxylate (m. p. 77°) which proved very difficult to remove. The following conditions were employed.

Magnesium turnings (20 g.) were treated with dry ethanol (45 ml.), and carbon tetrachloride (0·4 ml.) was added. Reaction commenced on slight warming and diethyl malonate (200 g.) in dry ethanol (200 ml.) was added with stirring and cooling. A few drops of mercury were introduced, and the mixture heated on a steam-bath for 90 min. and then cooled. Ethylene dibromide (58 g.) was added dropwise during 30 min. and the mixture heated and stirred for 12 hr. Volatile matter was removed under reduced pressure, ether (200 ml.) added, and the cooled mass decomposed with hydrochloric acid. The ether solution was washed with dilute acid, sodium hydrogen carbonate solution, and water. On drying, evaporation, and distillation, diethyl malonate (125·5 g.) was recovered (b. p. 53°/0·7 mm.; n_D^{18} 1·4151—1·4168).

The residue (60 g.) gave a strong colour reaction with ferric chloride : it was dissolved in ether (200 ml.) and the solution washed with N-potassium hydroxide and water : working up and distillation yielded material, b. p. 150—166°/1·8 mm., n_D^{26} 1·4378—1·4405 (46·1 g.). It still gave a red-purple ferric chloride reaction, and the above treatment with alkali was repeated. A series of fractions (total 40·0 g., 38%) was isolated by distillation (b. p. 154—165°/0·1 mm.; $n_D^{18·5}$ 1·4410—1·4413) : all gave only yellow or orange colours with ferric chloride.

The disodium derivative of one of these fractions (b. p. 154—160°/0·1 mm.; $n_D^{18·5}$ 1·4410; 15·6 g.) was prepared in dry ether (30 ml.) by adding sodium ethoxide, prepared from sodium (2·2 g.), dry ethanol (33 ml.), and ether (40 ml.). The salt was precipitated by the addition of more ether (230 ml.), filtered off, and washed with ether. Regeneration, by shaking it with hydrochloric acid (12 ml.) in water (24 ml.) and distillation, gave a sample (b. p. 130—146°/0·2 mm.) which crystallised (m. p. 13—17°) on the addition of a trace of impure tetraethyl *cyclo*hexane-1 : 1 : 4 : 4-tetracarboxylate. The material thus obtained was used to seed another of the fractions (b. p. 160—165°/0·1 mm.; $n_D^{18·5}$ 1·4410; 7·09 g.) which could then be crystallised as prisms (5·96 g.) (from ethanol at low temperature), m. p. 15—17°, b. p. 120—130°/0·2 mm. (bath temp.), n_D^{17} 1·4408 (Found : C, 55·5; H, 7·45; OEt, 52·2%; Sap. equiv., 86·0. Calc. for $C_{16}H_{26}O_8$: C, 55·5; H, 7·55; OEt 52·0%; Sap. equiv., 86·6).

It is likely that the enolic material which was removed during purification was diethyl 2-keto*cyclo*pentane-1 : 3-dicarboxylate or the triethyl 1 : 1 : 3-tricarboxylate. The extracted material gave intense purple colours with ferric chloride, and a copper enolate was isolated. The material may arise from the action of magnesium ethoxide on tetraethyl butane-1 : 1 : 4 : 4-tetracarboxylate. In support of this view, the ready cyclisation of the latter to diethyl 2-keto-*cyclo*pentane-1 : 3-dicarboxylate by hot sodium ethoxide (diethyl carbonate is eliminated) may be cited (Meincke, Cox, and McElvain, *loc. cit.*).

Butane-1 : 1 : 4 : 4-*tetracarboxylic Acid*.—The tetraethyl ester (m. p. 16—17°; 2·22 g.) was shaken with potassium hydroxide (1·84 g.) in water (8 ml.) for 12 hr. The product was concentrated under reduced pressure, acidified with hydrochloric acid (*ca.* 7 ml.), and then evaporated to dryness *in vacuo* at ≯40°. Continuous ether extraction (2 days) gave the tetra-acid (1·42

g., 95%) which was recrystallised from acetone–petroleum–ethyl acetate and then had m. p. 179° (with decarboxylation) (Found : C, 41·5; H, 4·45%; equiv., 61·3. Calc. for $C_8H_{10}O_8$: C, 41·05; H, 4·3%; equiv., 58·5). Decarboxylation gave adipic acid, m. p. 152°. Its *tetramethyl* ester, prepared with diazomethane like the others described below, crystallised from aqueous methanol or petroleum in long needles, m. p. 73·5—75·5° (Found : C, 49·75; H, 6·5; OMe, 42·65. $C_{12}H_{18}O_8$ requires C, 49·65; H, 6·25; OMe, 42·8%).

Tetraethyl Hexane-2 : 2 : 5 : 5-*tetracarboxylate*.—A mixture of tetraethyl butane-1 : 1 : 4 : 4-tetracarboxylate (3·5 g.; m. p. 14—17°) and methyl iodide (3·6 g.) was added to ice-cold sodium ethoxide, prepared from sodium (0·5 g.) and dry ethanol (10 ml.). The mixture was set aside (1½ hr.), refluxed (2 hr.), and evaporated. Water was added, the mixture extracted with ether, and the extract washed with dilute sodium thiosulphate solution, dried, and evaporated to give tetraethyl hexane-2 : 2 : 5 : 5-tetracarboxylate (3·44 g., 91%). On recrystallisation from light petroleum (b. p. 60—80°) this had m. p. 52·5—53·5° (3·17 g.).

The ester was hydrolysed at 25° as described under butane-1 : 1 : 4 : 4-tetracarboxylic acid except that a little ethanol was added and a longer reaction time allowed. Extraction of the residue after careful evaporation, anhydrous acetone being used, gave the tetra-acid (1·51 g.), m. p. 207° (with decarboxylation; bath pre-heated to 170° and heated rapidly). The m. p. after decarboxylation was 110—114° (mixture of stereoisomers). *Tetramethyl hexane*-2 : 2 : 5 : 5-*tetracarboxylate*, m. p. 93—94°, crystallised from aqueous methanol or petroleum (Found : C, 53·05; H, 7·15; OMe, 39·05. $C_{14}H_{22}O_8$ requires C, 52·8; H, 7·0; OMe, 39·0%).

Tetraethyl Propane-1 : 1 : 3 : 3-*tetracarboxylate*.—This was prepared according to the method of Caunt, Crow, Haworth, and Vodoz (*J.*, 1950, 1632), and had $n_D^{20\cdot5}$ 1·4387.

Tetraethyl Pentane-1 : 1 : 5 : 5-*tetracarboxylate*.—Guha and Seshadriengar's method (*Ber.*, 1936, **69**, 1215) gave a yield of 42% (based on 1 : 3-dibromopropane) of *ester*, b. p. 172°/0·08 mm., n_D^{19} 1·4452. This gave no colour with ferric chloride (Found: C, 55·6; H, 7·8%; Sap. equiv., 89·9. $C_{17}H_{28}O_8$ requires C, 56·65; H, 7·85%; Sap. equiv., 90·1).

The ester (5·36 g.) was hydrolysed at 25°, by shaking it with potassium hydroxide (3·70 g.) in water (15 ml.) for 35 hr., and then filtered off, acidified, and evaporated *in vacuo*. The residue was continuously extracted with ether. Evaporation yielded crude tetra-acid (3·40 g., 92·2%) which was stirred with petroleum, filtered, and crystallised from ethyl acetate–light petroleum (b. p. 60—80°), to give pentane-1 : 1 : 5 : 5-tetracarboxylic acid (1·84 g.), m. p. 155° (with decarboxylation; bath preheated to 110°) (Perkin and Prentice, *J.*, 1891, **59**, 824, give m. p. 125—130°). The product was faintly yellow (Found : C, 43·7; H, 5·15%; Neut. equiv., 64·8. Calc. for $C_9H_{12}O_8$: C, 43·55; H, 4·85%; Neut. equiv., 62·1). The *tetramethyl* ester crystallised in prisms from light petroleum (b. p. 60—80°), m. p. 42—43·5° (Found : C, 51·45; H, 6·7; OMe, 40·5. $C_{13}H_{20}O_8$ requires C, 51·3; H, 6·65; OMe, 40·8%).

Triethyl Butane-1 : 1 : 4-*tricarboxylate*.—(a) *From γ-butyrolactone*. A solution of the lactone (60 g.) in dry ethanol (200 ml.), was saturated with dry hydrogen bromide gas at 0°, more gas being passed in intermittently over 3 days. The mixture was set aside (12 hr.) and then briefly warmed at 100°, the solvent removed *in vacuo*, and ether (500 ml.) together with an excess of sodium hydrogen carbonate slurry added with cooling. The ether solution was worked up to give ethyl γ-bromobutyrate (112 g., 82%), b. p. 83°/12 mm., n_D^{22} 1·4553—1·4558.

This bromo-ester (39 g.) was condensed with ethyl sodiomalonate [from sodium (4·6 g.) and diethyl malonate] according to the directions of Boorman, Linstead, and Rydon (*J.*, 1933, 568). Refluxing of the vigorously stirred mass for 20 hr. was required to cause the sodium to react with diethyl malonate in benzene. When the bromo-ester had been added, boiling and stirring were continued for 28 hr. After the addition of water and ether, triethyl butane-1 : 1 : 4-tricarboxylate (72%), b. p. *ca.* 115°/0·1 mm., n_D^{20} 1·4364, was isolated in the usual way. Mild alkaline hydrolysis gave the corresponding tricarboxylic acid (90%), m. p. 148° (Montemartini, *loc. cit.*, gives m. p. 130°; Wislicenus and Schwanhäusser, *loc. cit.*, and Dieckmann, *Annalen*, 1901, **317**, 62, each give 139—140°).

(b) *From diethyl adipate*. Sodium (3·45 g.) was dissolved in dry ethanol (55 ml.), the excess of solvent removed, and the residue baked at 100°/0·1 mm. for 1 hr. Benzene (20 ml.) and then diethyl oxalate (21·9 g.) were added. When all the solid had dissolved, diethyl adipate (30·3 g.) was introduced in portions and the mixture set aside for 48 hr. It was poured into ice (300 g.) and hydrochloric acid (15 ml.), and the product isolated with ether, washed, dried, and evaporated. Decomposition by heating under nitrogen at 160—180°/20 mm. in a Kon flask packed with glass wool (1·5 hr.) gave, on isolation with ether and distillation, three fractions : (i) b. p. 66—120°/0·2 mm., n_D^{21} 1·4278 (8·2 g.); (ii) b. p. 120—126°/0·25 mm., $n_D^{20\cdot5}$ 1·4373 (18·5 g.); (iii) b. p. 126—150°/0·3 mm., $n_D^{20\cdot5}$ 1·4440 (6·05 g.).

Fraction (ii), impure ethyl butane-1 : 1 : 4-tricarboxylate, was thrice redistilled and then had n_D^{20} 1·4352 (Found : C, 57·25; H, 8·05; OEt, 49·65. Calc. for $C_{13}H_{22}O_6$: C, 56·9; H, 8·1; OEt, 49·25%). Triebs and Meyer (*Chem. Ber.*, 1952, **85**, 615) have recently reported a similar reaction giving a yield of 70%.

Diethyl 1-*Cyanobutane*-1 : 4-*dicarboxylate*.—The method of Gagnon, Gaudry, and King (*J.*, 1944, 13) was used except that the ethyl γ-bromobutyrate was added to ethyl sodiocyanoacetate in benzene. The product (35%) had b. p. 120°/0·15 mm., n_D^{26} 1·4389 (Found : C, 57·95; H, 7·65; N, 6·25. Calc. for $C_{11}H_{17}O_4N$: C, 58·1; H, 7·55; N, 6·15%). Some starting material was recovered and a high-boiling material also isolated. Triebs and Meyer (*loc. cit.*) give b. p. 118°/0·15 mm., n_D^{22} 1·4408.

Diethyl 1-*Cyanopentane*-1 : 5-*dicarboxylate*.—Interaction of ethyl δ-bromovalerate with ethyl sodiocyanoacetate in benzene gave only an 8% yield of material, b. p. 120°/0·2 mm., n_D^{23} 1·4416 (Found : C, 60·25; H, 8·1. Calc. for $C_{12}H_{19}O_4N$: C, 59·75; H, 7·95%). The ethyl δ-bromovalerate was isolated in a 32% overall yield by employing a slight adaptation of Büchi and Jeger's method (*loc. cit.*).

Reduction of Diethyl cyclo*Pentylidenecyanoacetate*-2-*acetate*.—This diester was prepared according to Linstead and Meade's method (*J.*, 1934, 941 : cf. Barrett and Linstead, *ibid.*, 1935, 440) and had b. p. 125—135°/0·02 mm. (bath temp.), n_D^{19} 1·4895. Linstead and Meade give n_D^{20} 1·4883, and Roberts and Gorham (*J. Amer. Chem. Soc.*, 1952, **74**, 2278) give n_D^{25} 1·4831.

Considerable difficulty was experienced in hydrogenating this sample. In ethanol solution, with 10% palladium–charcoal, absorption of hydrogen at atmospheric pressure ceased prematurely and was continued under pressure (5 atm.), but the product on distillation still contained unsaturated material. Little further reduction was accomplished by treatment with aluminium amalgam but finally, after treatment with Raney nickel in ethanol for a week, further absorption was achieved with a palladium–charcoal catalyst. The diethyl *cyclo*pentylcyanoacetate-2-acetate distilled at 132—138°/0·1—0·2 mm., and had $n_D^{21\cdot5}$ 1·4672—1·4676 (Linstead and Meade, *loc. cit.*, give n_D^{20} 1·4623, and Roberts and Gorham, *loc. cit.*, record n_D^{25} 1·4599).

cis-bicyclo[3 : 3 : 0]*Octan*-3-*one* 2 : 4-*Dinitrophenylhydrazone*.—The above ester, when treated with hydrobromic acid according to the standard technique described below, blackened, but yielded a ketonic fraction which gave *cis-bicyclo*[3 : 3 : 0]octan-3-one 2 : 4-dinitrophenylhydrazone, m. p. 114—115°, in 21% yield (Found : C, 55·65; H, 5·5. Calc. for $C_{14}H_{16}O_4N_4$: C, 55·25; H, 5·3%). Roberts and Gorham (*loc. cit.*) give m. p. 115—116°.

General Technique for the Acid-catalysed Cyclisation Experiments.—These experiments were conducted in a standardised one-piece apparatus, comprising a small reaction-flask surmounted by a Vigreux column and equipped with a nitrogen inlet and a means of adding more reagent. The mixture of ester or polycarboxylic acid (1 g.) and cyclising agent (*e.g.*, 1 : 1 hydrochloric acid–water; 2—3 ml.) was placed in the flask, heated in an oil-bath by means of an electric hot-plate and stirred by a fine stream of nitrogen bubbles. Steam-volatile ketone was carried out continuously with the aid of the nitrogen stream and collected in an excess of a 2 : 4-dinitrophenylhydrazine reagent [2 : 4-dinitrophenylhydrazine (2 g.), concentrated sulphuric acid (8 ml.), methanol (30 ml.), and water (10 ml.)]. The acid mixture was replenished as required from a teat-pipette.

After precipitation of most of the ketonic derivative, the nitrogen stream was stopped and the residual acid heated overnight at 120° (for experiments with hydrochloric acid) or 130° (hydrobromic acid), to ensure complete decarboxylation. During this period the surface of the dinitrophenylhydrazine reagent was arranged just to touch the end of the gas-exit tube. Next day the nitrogen was turned on and any remaining ketone forced over by heating and stirring for 1 hr. The dinitrophenylhydrazine reagent was cooled to 0°, and the derivative filtered off, dried, and chromatographed on alumina (Spence type H) from benzene. The yields of ketones are reported in the Table.

Estimation of the diacid formed by decarboxylation was made by evaporating the contents of the flask, drying the residue *in vacuo* over sodium hydroxide pellets, and weighing it.

Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a maintenance grant (to J. E. H. H.).

Imperial College of Science and Technology,
South Kensington, London, S.W.7.

[*Received, July* 12*th*, 1953.]

704. *The Anodic Oxidation of Metals at Very Low Current Density. Part II.* Nickel.*

By S. E. S. El Wakkad and (Miss) Sayeda H. Emara.

The conflicting results of various workers on the variation of the anode potential with the quantity of electricity passed when the nickel electrode is forced from evolution of hydrogen to that of oxygen, as well as on the type of oxides formed on the surface of the metal before oxygen evolution, have been clarified by carrying out the anodic oxidation of nickel in solutions of different pH values at very low current density. It is shown that the oxides formed on the anode before evolution of oxygen depend on the polarising current; at extremely low current density the oxides NiO, Ni_3O_4, Ni_2O_3, and NiO_2 are formed before oxygen is evolved, but at higher current density only the oxides NiO, Ni_2O_3, and NiO_2 appear. The primary anodic products are, however, the oxides NiO and NiO_2, Ni_3O_4 and Ni_2O_3 being formed from a secondary reaction between NiO and NiO_2. The higher oxides are unstable, decomposing to NiO, the most stable oxide in contact with the metal.

But little work has been carried out on the anodic oxidation of nickel. The results obtained are conflicting, and information on the type of oxide formed on the passive nickel is obscure. For instance, early observations on the nickel electrode in the Edison accumulator (Zender, *Z. Elektrochem.*, 1905, **11**, 809; 1906, **12**, 463; 1907, **13**, 572; Bellucci and Clavari, *Atti R. Accad. Lincei*, 1905, **14**, ii, 234; Grube and Vogt, *Z. Elektrochem.*, 1907, **13**, 572; 1938, **44**, 352; Foerster, *ibid.*, 1907, **13**, 414; 1908, **14**, 17, 285; 1910, **16**, 461) threw some doubt on whether Ni_2O_3 is formed primarly, and suggested that the main oxides formed on the nickel electrode are NiO and NiO_2, the oxides Ni_2O_3 and Ni_3O_4 being formed as solid solutions arising from interaction of NiO with NiO_2. On the other hand, the general conclusion reached from passivity studies (Evans and Stockdale, *J.*, 1929, 2651; Transtad, *Z. physikal. Chem.*, 1929, **142**, 272; Müller, *Monatsh.*, 1927, **48**, 559; Müller, Cameron, and Machu, *ibid.*, 1932, **53**, 73; Georgi, *Z. Elektrochem.*, 1932, **38**, 681, 714; 1933, **39**, 736) is that when nickel becomes passive it is covered with a protective film probably of the oxide Ni_2O_3 or the hydroxide $Ni(OH)_3$. Recently, Hickling and Spice (*Trans. Faraday Soc.*, 1947, **43**, 762), using the oscillographic method, showed that this oxide is the only one formed upon the metal anode before evolution of oxygen, and Besson (*Compt. rend.*, 1946, **223**, 28) showed that on nickel anodes NiO, Ni_3O_4, and Ni_2O_3 were formed but he found no evidence for NiO_2. VolchKova, Antonova, and Krasil'Shchikov (*J. Phys. Chem., U.S.S.R.*, 1949, **23**, 714) showed also that $Ni(OH)_2$ and Ni_2O_3 were formed on nickel anodes and that at high voltages oxygen is liberated on Ni_2O_3.

This matter has now been clarified by studying the anodic oxidation of nickel at very low current density, the technique and procedure developed for platinum (Part I, *loc. cit.*) being used. In this case attention has been directed primarily to the behaviour of nickel in alkaline solutions, where passivity is set up almost at once. From this study it is shown that, when nickel is forced from the hydrogen-evolution potential to the value for oxygen evolution, the oxides formed on the anode before oxygen is evolved depend on the polarising current. Although at extremely low current density the oxides NiO, Ni_3O_4, Ni_2O_3, and NiO_2 were formed before oxygen evolution, yet at higher current density only NiO, Ni_2O_3, and NiO_2 appeared. The primary anodic products are, however, the oxides NiO and NiO_2, the other oxides being formed from them by a secondary reaction. The higher oxides are unstable, decomposing to NiO, which is the most stable oxide in contact with the metal.

Experimental

The electrical circuit and the electrolytic cell used were as previously described (Part I, *loc. cit.*). The nickel electrodes used were prepared by electrodeposition at a current of 20 mA/electrode for 30 min. from a bath containing, per l., $NiSO_4,6H_2O$ (300 g.), NaCl (3 g.), and H_3BO_3 (6 g.) on a platinum plate of 1·95 sq. cm. apparent area. The same results were obtained

* Part I, *J.*, 1952, 461.

if nickel was deposited on platinum previously plated with copper. The electrode was washed several times in conductivity water and then with the solution in which it was to be studied, before it was placed in its compartment in the electrolytic cell. Each experiment was carried out with a freshly prepared electrode. The cathode was a platinum spiral placed in such a position as to ensure uniform distribution of the polarising current at the anode surface.

Measurements were carried out mainly in the alkaline solutions, 0·1N-sodium hydroxide (pH 13), N-sodium carbonate (pH 11·5), and 0·1N-borax (pH 9·2). Anodic polarisations were carried out also in acetate buffer mixture of pH 5·6 (Cohn, *J. Amer. Chem. Soc.*, 1927, **49**, 173; 1928, **50**, 696). The solution was boiled before use and cooled in an atmosphere of pure nitrogen to remove any dissolved oxygen.

The detailed experimental procedure for obtaining the anodic, the cathodic, and the decay curves was essentially as described in Part I (*loc. cit.*). Two different polarising currents were used in the anodic polarisation, namely, 5 and 15 μA per electrode. The e.m.f. measurements were carried out exactly as for platinum (*loc. cit.*).

Measurements of the Oxide Potentials of Nickel.—The reports of previous workers on the different oxides of nickel are not in agreement. Bellucci and Clavari (*loc. cit.*) found that the degree of oxidation of nickel depended on the nature of the oxidising agent used and that none of these reagents led to the formation of an oxide having a formula Ni_2O_3. On oxidation with bromine in the presence of excess of potassium carbonate at 0°, and on washing the precipitate with concentrated potassium carbonate solution, the ratio Ni : O was 1 : 1·907, *i.e.*, nearly that required for NiO_2. This oxide was found to lose oxygen, forming substances of composition varying with the conditions. When NiO_2 was dried over calcium chloride at 100°, it passed almost always into a substance in which the Ni : O ratio varied from 1 : 1·4 to 1 : 1·3. The authors therefore regarded the oxides Ni_2O_3 and Ni_3O_4 as mixtures of NiO_2 and NiO.

On the other hand, Howell (*J.*, 1923, **123**, 669, 1772), by following the rate of decomposition of the precipitate obtained by the action of alkali and hypochlorite on nickel sulphate solution, found that in general the precipitate consisted of the hydroxide $Ni(OH)_2$, the sesquioxide, and the dioxide, but with sufficient hypochlorite the whole of the nickelous hydroxide was oxidised to the other two oxides.

We prepared the oxides NiO, Ni_3O_4, and NiO_2 by recommended methods (Archibald, "The Preparation of Pure Inorganic Substances," New York, 1932, p. 349; Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Vol. 15, Longmans Green and Co., 1947, pp. 391, 392).

Potential Measurements.—For these measurements a portion of the oxide was shaken with 0·1N-sodium hydroxide solution, and in measuring the potentials of systems containing NiO, a short nickel electrode was wholly immersed in the sludge formed and the potential was measured against a saturated calomel electrode in an atmosphere of pure nitrogen. When the oxidation–reduction potential between the two oxides, Ni_3O_4 and Ni_2O_3, was measured, the oxides were mixed in the 0·1N-sodium hydroxide solution, and a short platinum wire electrode was wholly immersed in the sludge formed; the potential was also measured in an atmosphere of pure nitrogen against a saturated calomel electrode. All the electrical measurements were carried out in an air thermostat at 25° ± 0·01°.

Results and Discussion

In Fig. 1, curve *A* is the characteristic anodic polarisation curve of nickel at 25° with a polarising current of 5 μA per electrode in 0·1N-sodium hydroxide. Curve *A'* is the anodic polarisation curve in the same solution but with a polarising current of 15 μA per electrode. In Fig. 2, Curves *A* and *A'* are the same anodic polarisation curves in 0·1N-sodium carbonate solution of pH 11·5. From these curves it can be seen that nickel gives characteric anodic polarisation curves in which we can detect the following stages: (1) a rapid linear rise of potential; (2) a somewhat slow rise of potential accompanied by five or by four steps according as the polarising current is 5 or 15 μA per electrode.

The first stage can be attributed, as in previous cases (Hickling and Spice, *Trans. Faraday Soc.*, 1947, **43**, 762), to the charging of the double layer. Measurements from a large number of polarisation curves in 0·1N-sodium hydroxide gave an average value of the double layer capacity of about 900 μF per apparent sq. cm. for our nickel electrode, and in N-sodium carbonate the average value was about the same. The nature of the second stage is very important, since the number of steps depended upon the polarising current used.

The Oxide Potentials of Nickel.—In Table 1 are shown the results obtained for the potentials of the different systems of nickel oxides on the hydrogen scale in 0·1N-sodium

TABLE 1.

System	Ni–NiO	$NiO–Ni_3O_4$	$Ni_3O_4–Ni_2O_3$	$Ni_2O_3–NiO_2$	NiO–NiO_2
Potential (v) in 0·1N-NaOH	−0·60	−0·35	+0·15	+0·47	+0·55

hydroxide. The potentials of the first three systems are our direct experimental measurements, that of the fourth system is a calculated value at the corresponding pH from a knowledge of the potential of the systems $Ni(OH)_2–NiO_2$ (Foerster, *loc. cit.*) and $Ni(OH)_2–Ni_2O_3$ (Hickling and Spice, *loc. cit.*), and that of the last system is due to Foerster (*loc. cit.*).

FIG. 1.

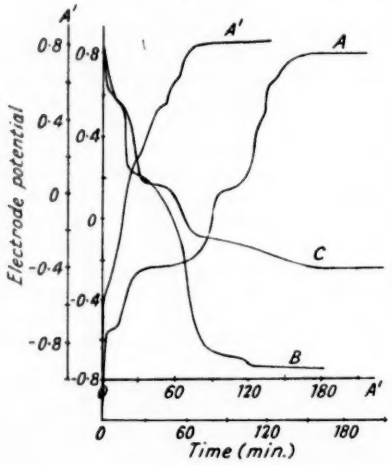
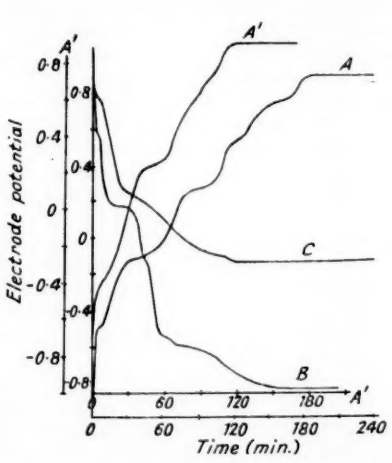


FIG. 2.



In Table 2 the starting potentials of the various steps observed under different polarising conditions (see above) are compared with the potentials of the same five systems at the corresponding pH values. The agreement between the determined equilibrium potentials and the starting potentials of the first four steps in our polarisation curves when using a polarising current of 5 μA per electrode suggests that these steps correspond to the

TABLE 2.

Solution	Ni–NiO	$NiO–Ni_3O_4$	$Ni_3O_4–Ni_2O_3$	$Ni_2O_3–NiO_2$	NiO–NiO_2
		Equilibrium potentials			
0·1N-NaOH	−0·60	−0·35	+0·15	+0·47	+0·55
N-Na_2CO_3	−0·51	−0·26	+0·24	+0·56	+0·64
	Starting potentials (v) of steps with polarising current of 5μ amp.				
0·1N-NaOH	−0·58	−0·32	+0·13	+0·45	+0·61
N-Na_2CO_3	−0·51	−0·20	+0·24	+0·50	+0·70
	Starting potentials (v) of steps with polarising current of 15μ amp.				
0·1N-NaOH	−0·58	—	+0·15	+0·45	+0·60
N-Na_2CO_3	−0·48	—	+0·20	+0·55	+0·67

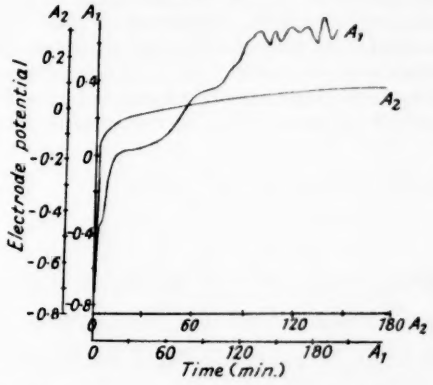
consecutive formation of the oxides NiO, Ni_3O_4, Ni_2O_3, and NiO_2 on the nickel anode before evolution of oxygen. The nature of the fifth step is discussed on p. 3507.

The quantity of electricity passed in the first step was about 1200 μcoulomb/apparent sq. cm., which would correspond to the formation of $3·75 \times 10^{15}$ atoms of oxygen; the density of nickel being taken as 8·8, the diameter of the nickel atom may be calculated as approximately $2·2 \times 10^{-8}$ cm., and hence there would be about 2×10^{15} atoms of metal per true sq. cm. A rather crude estimate of the ratio of the real to the apparent area of our

nickel electrode can be obtained from the value of the capacity of the double layer at the electrode in 0·1N-sodium hydroxide solution. The capacity of the double layer at platinum anodes before formation of oxide as obtained from previous studies (Hickling, *Trans. Faraday Soc.*, 1945, **41**, 333; Part I, *loc. cit.*) can be estimated as 100 μF per true sq. cm. If the difference between the capacity of our nickel electrode and the platinum electrode is assumed to be due only to the difference in the area, the ratio of the real to the apparent area of our nickel electrode will be about 9. This shows that the quantity of electricity passed in the first step corresponds to the formation of less than a unimolecular layer of NiO on the surface of the nickel. In this respect nickel is similar to cobalt (El Wakkad and Hickling, *Trans. Faraday Soc.*, 1950, **46**, 820). This fact may explain the agreement between the potential of the second step when using a polarising current of 5 μA per electrode with the experimentally determined value of the system NiO–Ni_3O_4 when using a nickel electrode.

The quantity of electricity passed in the second step was about 6000 μcoulomb/apparent sq. cm., which would liberate about 9×10^{15} atoms oxygen; this suggests that an approximately unimolecular film of Ni_3O_4 is formed. The quantity of electricity passed

FIG. 3.



in the third step was about 13,500 μcoulombs/apparent sq. cm., which is enough for the liberation of $4{\cdot}2 \times 10^{16}$ atoms of oxygen. This suggests that nickelic oxide is about two molecules thick. The nickelic oxide is further oxidised to the dioxide NiO_2.

On the other hand when using a polarising current of 15 μA/electrode (Figs. 1 and 2, curves *A'*) we get in the second stage four steps instead of five. From Table 2, the first three steps correspond to the formation of the oxides NiO, Ni_2O_3, and NiO_2. The nature of the last step is discussed on p. 3508.

The interesting fact that the numbers of steps differ according as the polarising current is 5 or 15 μA/electrode can be explained by consideration of the work of Bellucci and Clavari and of Foerster (*locc. cit.*), in which they considered that the oxide Ni_3O_4 is a solid solution or an oxide formed from a secondary reaction between NiO and NiO_2; for, at the very low current density, where the rate of discharge of hydroxyl ions is very small compared with the rate of combination between the oxides to form Ni_3O_4, this oxide will appear on the anodic polarisation curve. On the other hand, when the polarising current is increased to 15 μA/electrode and the rate of discharge of hydroxyl ions becomes higher than the rate of combination, the formation of the oxide Ni_3O_4 is greatly suppressed, and we get directly Ni_2O_3. The oxide Ni_2O_3 was considered also (Bellucci and Clavari, *loc. cit.*) to be a mixture of NiO and NiO_2; the results obtained, however, indicate that the rate of its formation must be higher than the rate of discharge of hydroxyl ions when a polarising current of 15 μA/electrode is used. If the polarising current is increased further, so that the rate of discharge of hydroxyl ions becomes still higher, a stage may be reached at which Ni_2O_3 will not appear and the anodic process will lead directly to the formation of NiO_2 after

NiO. We attempted an experiment at such a higher current density, but unfortunately the changes in the anodic potential were too rapid to be recorded by our direct potentiometric method.

The nature of the last step in the anodic polarisation curves is very interesting and may throw some light on this point, for comparison of the potential of this step with all the known oxidation–reduction potentials between the different oxides of nickel shows it to be near that of the system NiO–NiO_2, thus confirming the view that the NiO and NiO_2 are the primary oxidation products at a nickel anode. The oxide Ni_3O_4, and to some extent Ni_2O_3, are formed in secondary reactions between NiO and NiO_2.

The cathodic curves (*B* in Figs. 1 and 2) indicate reduction of the oxides NiO_2,Ni_2O_3, and NiO. There is no step corresponding to the reduction of the oxide Ni_3O_4.

The decay curves (*C* in Figs. 1 and 2) indicate clear steps at the potential of +0·60 and +0·15 v in the 0·1N-sodium hydroxide solution and at +0·70 and 0·25 v in N-sodium carbonate. Thus decay curves indicate that both NiO_2 and Ni_2O_3 are unstable. The decay curves in all cases approach very slowly the Ni–NiO potential, which is reached after about 24 hr. This shows that the latter oxide is the most stable one on the metal surface.

In the borate solution (curve *A*, Fig. 3) the potentials of the steps formed after the charging of the double layer indicate the formation of NiO, Ni_3O_4, and Ni_2O_3 on the electrode surface, after which the potential became irregular, indicating that the film formed subsequently (which may be a basic borate) is non-adherent and peals away. In more acid solutions, *i.e.*, in acetate buffer of pH 5·6 (curve A_2, Fig. 3) the electrode potential never rises to that of oxygen evolution, but the curve shows only anodic dissolution of the metal.

CAIRO UNIVERSITY, FACULTY OF SCIENCE, CAIRO, EGYPT. [*Received, April 13th*, 1953.]

705. *The Anodic Oxidation of Metals at Very Low Current Density. Part III.* Copper.*

By S. E. S. EL WAKKAD and (MISS) SAYEDA H. EMARA.

The anodic oxidation of copper at very low current density is examined primarily in alkaline solutions where passivity takes place more readily. It is shown that when copper is forced from the hydrogen evolution potential to the oxygen evolution value, cuprous oxide is formed as a layer 4—5 molecules thick, and then part of this film is oxidised to cupric oxide or hydroxide. No evidence has been obtained for the formation of Cu_2O_3 as suggested by Müller. In solutions of pH 5·6 the anode never rises to the oxygen evolution potential. The anodic oxidation in such solutions containing copper ions of different concentrations has been studied as well, and the behaviour has been explained.

IN continuation of previous work (El Wakkad and Emara, *J.*, 1952, **461**), the anodic oxidation of copper at very low current density has been investigated. No work on copper from the present standpoint has been published, but studies under different conditions have yielded relevant information; *e.g.*, copper normally dissolves when made the anode in acid solutions but may become passive if conditions are such that a film of a sparingly soluble salt is formed on the surface, this being followed by production of a more protective oxide film which in general appears to be cuprous oxide, although cupric oxide is also formed under strongly oxidising conditions (Fischer, *Z. Elektrochem.*, 1903, **9**, 507; *Z. phys. Chem.*, 1904, **48**, 177; Shukoff, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 1253). Müller (*Z. Elektrochem.*, 1907, **13**, 133) investigated the anodic behaviour of copper in very concentrated sodium hydroxide solutions and suggested that Cu_2O, CuO, and Cu_2O_3 are formed on the copper anode before oxygen evolution (see also Müller and Spitzer, *ibid.*, p. 27).

* Part II, preceding paper.

The oxide Cu_2O_3 was considered to be unstable and decomposed to give oxygen and cupric oxide. Hickling and Taylor (*Trans. Faraday Soc.*, 1948, **44**, 262) on the other hand, using the oscillographic method, showed that the anodic polarisation at a copper anode in sodium hydroxide solutions was accompanied by formation of an oxide film on the anode. Cuprous oxide was initially formed but was almost at once oxidised to cupric oxide. With buffer solutions of progressively decreasing alkalinity the formation of a sparingly soluble salt preceded or accompanied the formation of the oxide film. In acid solutions giving soluble copper salts a copper anode did not become satisfactorily passive and the anodic process was merely the dissolution of copper.

From measurements on the equilibrium potentials of copper in solutions of different pH values, Tourky and El Wakkad (*J.*, 1948, 740, 749) and El Wakkad (*J.*, 1950, 3563) showed that cuprous oxide is formed on the surface of copper and that this oxide is the stable one on the surface of the metal. Numerous investigations have been made on the nature of the partially protective film formed when a fresh copper surface is exposed to, or heated in, air or oxygen (Hinshelwood, *Proc. Roy. Soc.*, 1923, **102**, 318; Evans, *J.*, 1925, **127**, 2491; Vernon, *J.*, 1926, 2273; Constable, *Proc. Roy. Soc.*, 1927, **115**, 570; Thomson, *ibid.*, 1930, **128**, 654; Murison, *Phil. Mag.*, 1934, **17**, 96; Campbell and Thomas, *Trans. Electrochem. Soc.*, 1939, **76**, 303); the results obtained seem to indicate that the film primarily formed is one of cuprous oxide, although cupric oxide may also be present particularly in films formed at high temperatures or by prolonged heating.

In the present investigation attention has been directed primarily to the behaviour of copper in alkaline solutions where passivity takes place more readily. It is shown that when copper is forced from the hydrogen evolution potential to the oxygen evolution value, cuprous oxide is first formed as a layer 4—5 molecules thick and then part of this film is oxidised to cupric oxide or hydroxide. No evidence has been obtained for the formation of Cu_2O_3 (see above). In comparatively acid solution (pH 5·6) the anode never rises to the oxygen evolution potential. The anodic behaviour in such solutions containing copper ions of different concentrations has also been studied, and it is found that when Cu^{++} ions are present in such acid solutions, oxidation to the cupric oxide stage can take place provided that the concentration of the Cu^{++} ions is not less than 0·0002M. This behaviour is explained by taking into consideration the solubility product of cuprous oxide and the cuprous–cupric equilibrium at the surface of metallic copper.

Experimental

The electrical circuit and the electrolytic cell used were as previously described (El Wakkad and Emara, *loc. cit.*). The copper electrodes were prepared by electrodeposition from acidified copper sulphate solution. The deposition was made on a platinum plate of 1·95 sq. cm. area by a current of 25 mA/electrode for 30 min. The electrode was washed several times in conductivity water and then with the solution under investigation before it was introduced into the electrolytic cell. Each experiment was carried out with a freshly prepared electrode. The anode was placed in such a position with respect to the cathode as to ensure uniform distribution of the polarising current at the anode surface. The cathode was a platinum spiral about 10 cm. long and 0·1 cm. in diameter.

Measurements were carried out mainly in alkaline solutions, *viz.*, 0·1N-sodium hydroxide (pH 13), 1N-sodium carbonate (pH 11·5), and 0·1M-sodium borate pH 9·2), and also in an acetic acid–sodium acetate buffer of pH 5·6. The solution in the cell was boiled before use and cooled in an atmosphere of pure nitrogen to remove dissolved oxygen.

The polarising currents used were 20 μA per electrode for the borate and carbonate solutions and 50 μA per electrode for the sodium hydroxide solution. In each solution three phenomena were investigated for each electrode: anodic polarisation, cathodic polarisation, and anodic decay. The procedure adopted in obtaining the corresponding curves was as described for platinum (El Wakkad and Emara, *loc. cit.*).

The reference half-cell was a saturated calomel electrode prepared as described before (*idem, loc. cit.*). The electrolytic cell and the reference half-cell were kept in an air thermostat at 25° ± 0·01°. The e.m.f. was measured with a calibrated meter bridge and an Onwood mirror galvanometer having a sensitivity of 190 mm. per microamp. All potentials quoted are on the hydrogen scale.

Results and Discussion

Curve *A*, Fig. 1, is the characteristic anodic polarisation curve of copper at 25° with a polarising current of 20 μA, in 0·1M-sodium borate (pH 9·2). Curve *A*, Fig. 2, is the same anodic polarisation curve in N-sodium carbonate (pH 11·5), and curve *A*, Fig. 3 is the anodic polarisation curve of copper with a polarising current of 50 μA in 0·1N-sodium hydroxide (pH 13). From these curves, which show the variation in the potential of the copper anode with the quantity of electricity passed, it can be seen that at first there is a rapid initial build-up of potential (ascribable to the charging of the double layer as in previous studies, El Wakkad and Emara, *loc. cit.*) which is followed by two well-defined arrests before oxygen evolution. Measurements from a larger number of polarisation curves in 0·1M-sodium borate gave an average value of double-layer capacity of 900 μF per apparent sq. cm. of our copper electrode; in N-sodium carbonate, this value was also 900 μF, and in 0·1N-sodium hydroxide it was 1300 μF. The standard condition in this case was taken as that in the borate solution, since (see p. 3511) cuprous and cupric oxides are formed over the copper anodes before oxygen evolution, and these oxides are amphoteric. The isoelectric region, *i.e.*, that of minimum solubility, is in the slightly alkaline pH range, represented in

Fig. 1.

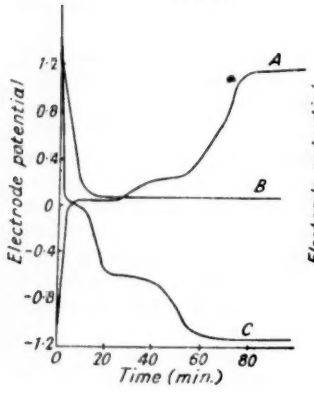


Fig. 2.

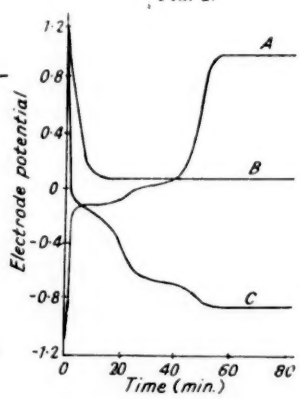
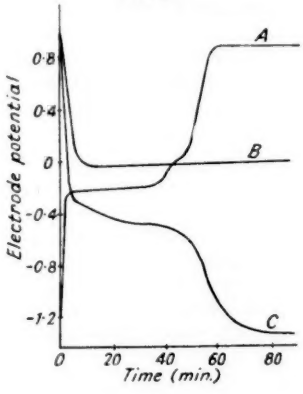


Fig. 3.



this case by the borate buffer solution (Tourky and El Wakkad, *loc. cit.*; McDowell and Johnston, *J. Amer. Chem. Soc.*, 1936, **58**, 2009).

The first arrest after the charging of the double layer appears to start at a potential of −0·04 v in 0·1M-sodium borate, at −0·19 v in N-sodium carbonate, and at −0·28 v in 0·1N-sodium hydroxide. The second arrest appears to start at potentials of +0·19, +0·03, and −0·03 v in the three solutions respectively. In the table are shown the starting potentials for these two arrests in various electrolytes compared with the equilibrium potentials of the systems $Cu–Cu_2O$, $Cu_2O–CuO$, and $Cu_2O–Cu(OH)_2$. These equilibrium potentials were obtained as follows.

The free energy of cuprous oxide, OH^-, and H_2O being taken as −35,150, −37,585, and −56,690 cal. (Latimer, "The Oxidation States of the Elements and their Potentials in Aqueous Solutions," New York, 1938, p. 35, 170), the free-energy change of the reaction $2OH^- + 2Cu = Cu_2O + H_2O + 2e$ is $\Delta F = -16{,}670$ cal., and hence E_B^0 (the potential value at the extreme alkaline range of pH) is −0·361 v at 25°. By taking the free energy of CuO as −30,400 cal. (Latimer, *op. cit.*) the free-energy change of the rection $Cu_2O + 2OH^- = 2CuO + H_2O + 2e$ is $\Delta F = -7170$ cal., and hence E_B^0 is −0·156 v at 25°. Also by taking the free energy of $Cu(OH)_2$ as −85,500 cal. (*idem, ibid.*), the free energy of the reaction $Cu_2O + 2OH^- + H_2O = 2Cu(OH)_2 + 2e$ is $\Delta F = -3990$ cal., and E_B^0 is −0·087 v. By applying the ordinary equation for the variation of the potential of these systems with pH, the values shown in cols. 4, 5, and 6 of the table were obtained.

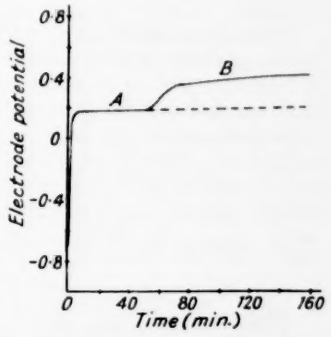
The very close agreement between the starting potential of the first and the second

arrests and the equilibrium values for the systems $Cu–Cu_2O$ and $Cu_2O–Cu(OH)_2$ leaves little doubt that these two steps in the anodic polarisation in such solutions correspond to the consecutive formation of cuprous oxide and cupric hydroxide. There is no step corresponding to the formation of a higher oxide (Cu_2O_3) as suggested by Müller (*loc. cit.*).

Solution	Starting potential (v) of: first arrest	second arrest	Equilibrium potential (v) of system: $Cu–Cu_2O$	$Cu_2O–CuO$	$Cu_2O–Cu(OH)_2$
0·1N-NaOH	−0·28	−0·03	−0·30	−0·10	−0·03
N-Na_2CO_3	−0·19	+0·03	−0·21	−0·01	+0·05
0·1M-$Na_2B_4O_7$ ...	−0·04	+0·19	−0·07	+0·13	+0·19

The quantity of electricity passed from the beginning of the first step to the end was, in sodium borate and sodium carbonate solutions, about 12,300 microcoulombs per apparent sq. cm. This is sufficient for the liberation of about $3·9 \times 10^{16}$ atoms of oxygen. The specific gravity of copper being taken as 8·9, the diameter of the copper atom ma be calculated to be $2·28 \times 10^{-8}$ cm., and hence there would be about $1·93 \times 10^{15}$ atoms per true sq. cm. at a copper surface. A rather rough estimate for the ratio of the real to the apparent area of the copper electrode under investigation can be obtained from the value of the capacity of the double layer at the electrode under the standard conditions. The capacity of the double layer of platinum anodes before oxide formation as obtained from previous studies (Hickling, *Trans. Faraday Soc.*, **1945**, **41**, 333; El Wakkad and Emara, *loc. cit.*) can be estimated as 100 μF per true sq. cm. If the difference between the capacity of the copper electrode and platinum electrode is assumed to be due only to the difference in the area, the ratio of the real to the apparent area of our copper electrode will be about 9. This shows that the quantity of electricity passed in the first step corresponds to the formation of a Cu_2O film some 4—5 molecules thick. The quantity of electricity passed from the beginning of the first step to the end in the case of the sodium hydroxide solution was much larger than the above, *viz.*, 46,000 microcoulombs per apparent sq. cm.; this is, however, in harmony with the known fact that the solubilities of both cuprous and cupric oxides increase in such comparatively strongly alkaline solutions The quantity of electricity passed in the second step in the case of the borate solution was 10,300 microcoulombs per apparent sq. cm., but in the carbonate and sodium hydroxide solutions it was 6000 microcoulombs. This suggests that the film of $Cu(OH)_2$ formed was less than the Cu_2O, or that part of Cu_2O film initially present in contact with the metal had been oxidised to $Cu(OH)_2$ before oxygen evolution. This view is further confirmed by both the decay and the cathodic curves (curves *B* and *C*, respectively, in Figs. 1, 2, and 3). The decay curves *B* reveal that on interruption of the polarising current when the copper anode was at the oxygen evolution potential, the potential fell to that of the system $Cu_2O–Cu(OH)_2$, whereat it remained constant and did not fall to that of the $Cu–Cu_2O$ system. It is known that the Cu–CuO or $Cu–Cu(OH)_2$ system is always unstable (specially in alkaline solutions) owing to the reduction of CuO to Cu_2O (Britton, *J.*, 1925, **127**, 2796; Allmand, *J.*, 1909, **95**, 2151). The stability of the electrode potential at the $Cu_2O–Cu(OH)_2$ potential indicates, therefore, that the cupric hydroxide is not in direct contact with the metal.

FIG. 4.



In the cathodic curves there are two distinct steps which are expected to correspond to the reduction of cupric hydroxide and cuprous oxide. The potentials of these steps are, however, displaced to more negative values than the reversible potentials of the $Cu_2O–Cu(OH)_2$ and $Cu–Cu_2O$ systems. The same observations were made also by Hickling and Taylor (*loc. cit.*). This behaviour in the reduction process can be explained by taking into consideration the view expressed before, *viz.*, that in the anodic polarisation most of the cuprous oxide is oxidised to $Cu(OH)_2$. Owing to the comparatively high resistance of both cuprous and cupric oxides or hydroxides, and as the oxide films here are not very protective, it

can be imagined that in the cathodic polarisation reduction starts at the metal surface and that the section of the very thin film of Cu_2O in contact with the metal is reduced first. The freshly formed metallic surface will therefore come into contact with the outer thick layer of cupric hydroxide. As this happens, there will be a transient tendency for the more positive potential of Cu_2O–$Cu(OH)_2$ to be restored, but this is rapidly levelled down as reduction proceeds further. The difference in potential between the systems Cu–Cu_2O and Cu–$Cu(OH)_2$ is only about 0·1 v, and it can be expected that, at this stage, the reduction of both Cu_2O and $Cu(OH)_2$ will take place. The second step in the cathodic curves, which occurs at a very negative value and approximately at the same potential in all solutions, may be due to the presence of very small amounts of copper dissolved, probably as cuprite ions (Tourky and El Wakkad, *loc. cit.*).

In the case of more acid solutions, *i.e.*, acetate buffer of pH 5·6 (curve *A*, Fig. 4), the copper anode never rose to the value of oxygen evolution potential but remained constant at 0·19 v. This is the value for Cu–Cu_2O at the corresponding pH, which indicates that the cuprous oxide formed possesses a very high solubility in such a solution. When copper sulphate was added to such a solution, the shape of the curve did not change until the solution became about 0·0002M with respect to Cu^{++} ions, after which it rose to *B* (Fig. 4) starting at the potential +0·35 v, which is the Cu_2O–CuO potential at the corresponding pH value.

These observations can be explained by taking into consideration the solubility product of cuprous oxide and the cuprous and cupric equilibrium at the surface of metallic copper : the solubility product of cuprous oxide being taken as $7{\cdot}18 \times 10^{-14}$ (Tourky and El Wakkad, *loc. cit.*) and the equilibrium constant of the reaction $Cu + Cu^{++} = 2Cu^{+}$ as 1×10^{-5} from El Wakkad's recent work (*loc. cit.*), a solution of pH 5·6 and 0·0002M with respect to Cu^{++} ions will lead directly to the formation of cuprous oxide over metallic copper when this metal is dipped in such a solution. The anodic polarisation under these conditions will lead therefore to the oxidation of Cu_2O to CuO, as has been found experimentally.

Cairo University, Faculty of Science, Cairo, Egypt. [*Received, April 13th*, 1953.]

---

706. p-*Menthane*-2 : 3-*diols. Part II.** *Catalytic Hydrogenation of Diosphenol and Reduction by Sodium and Ethanol.*

By A. Killen Macbeth and W. G. P. Robertson.

Reinvestigation of the reduction of diosphenol by sodium and ethanol has confirmed the production of (±)-menthol and a mixture of stereoisomeric glycols. One of the diols previously obtained has been more fully characterised; and a second glycol has been isolated in a pure state. Catalytic hydrogenation of diosphenol at laboratory temperatures yields substantially only one glycol and it is related to (±)-*neoiso*menthol. The additional data now available enable tentative configurations to be assigned to most of the racemic *p*-menthane-2 : 3-diols.

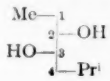
A synthesis of diosphenol in good yield from menthone, through 2-hydroxymenthone, is described.

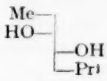
In Part I* a system of nomenclature for the eight stereoisomeric racemic *p*-menthane-2 : 3-diols was proposed, and the isolation of two glycols which were considered to be (±)-*cis*-2-hydroxymenthol and (±)-*cis*-2-hydroxy*iso*menthol was described. In addition, five other diols were isolated, but as configurations could not definitely be assigned to the compounds they were referred to as glycols A, B, C, D, and E. Further work now enables configurations to be suggested in most cases.

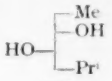
The reduction of diosphenol by Kondakov and Bachtschiev (*J. pr. Chem.*, 1901, **63**, 49) yielded (±)-menthol and a mixture from which a crystalline glycol, m. p. 92°, was obtained. This was later shown to be a *p*-menthane-2 : 3-diol (Semmler and McKenzie, *Ber.*, 1906,

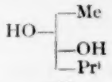
* Part I, Macbeth and Robertson, *J.*, 1953, 895.

39, 1160) as it gave α-methyl-α′-*iso*propyladipic acid on oxidation. Reduction of diosphenol with sodium and ethanol has now been shown to give a mixture of stereoisomeric glycols in yield of more than 60%. Fractional distillation of the viscid reduction product gave a forerun which contained (±)-menthol, and this was followed by a glycol fraction, a colourless very viscid oil which partly crystallised. Purification of the glycol itself, or through its di-*p*-nitrobenzoate, gave the pure diol, m. p. 91°, which is doubtless identical with that


(I)


(II)

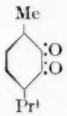

(III)


(IV)

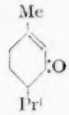
previously prepared by Kondakov and Bachtschiev (*loc. cit.*). The di-*p*-nitrobenzoate, m. p. 118°, is identical with the similar ester of glycol B previously obtained by the per-acid hydroxylation of (±)-*trans*-*p*-menth-2-ene (see Part I, *loc. cit.*). On the basis of its preparation by the *trans*-hydroxylation of (±)-*trans*-*p*-menth-2-ene glycol B must have one of the configurations (I) or (II) : and in view of the fact that sodium and ethanol reduction of 2-alkyl*cyclo*hexanones gives essentially the *trans*-alcohol there is justification for concluding that the glycol, m. p. 91°, previously described as glycol B, is (±)-*trans*-2-hydroxymenthol (I) rather than (±)-*trans*-2-hydroxy*neo*menthol (II). The latter configuration is consequently assigned to glycol A, m. p. 79°, the other of the pair of diols obtained by the *trans*-hydroxylation of (±)-*trans*-*p*-menth-2-ene.

The syrup recovered after the separation of (±)-*trans*-2-hydroxymenthol was converted into the di-*p*-nitrobenzoate, and a pure ester, m. p. 166°, was obtained by fractional crystallisation from ethanol. This was found to be identical with the previously described di-*p*-nitrobenzoate from glycol E, and on hydrolysis gave a diol, m. p. 77°, which showed no depression on admixture with glycol E itself. As the latter was obtained by per-acid *trans*-hydroxylation of *cis*-*p*-menth-2-ene, it has either of the configurations (III) or (IV); and as it is obtained by the sodium and ethanol reduction of diosphenol it is concluded that glycol E is (±)-*trans*-2-hydroxy*iso*menthol (III). The alternative configuration (IV) is accordingly assigned to one of the other diols obtained in the *trans*-hydroxylation of *cis*-*p*-menth-2-ene, and glycol D, m. p. 69°, is believed to be (±)-*trans*-2-hydroxy*neoiso*menthol. This is necessarily tentative, as three glycols were obtained in the per-acid hydroxylation one of which (glycol C) was believed to be a 3 : 4-diol derived from *p*-menth-3-ene present as an impurity.

The assumptions that glycol B is *trans*-2-hydroxymenthol (I) and that glycol E is *trans*-2-hydroxy*iso*menthol (III) receive some support from the fact that sodium and ethanol reductions of piperitone, menthone, and *iso*menthone give rise to menthol and *iso*menthol (Read and Cook, *J.*, 1925, **127**, 2784; Hughesdon, Read, and Smith, *J.*, 1923, **123**, 2918). The similarity between the formulæ for diosphenol (V*a*, V*b*), pipertone (VI), menthone (VII), and *iso*menthone (VIII) suggests that under the same conditions their reductions might well follow similar stereochemical paths.


(V*a*)

(V*b*)

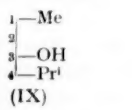

(VI)

(VII)

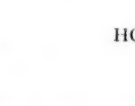
(VIII)

Catalytic hydrogenation of diosphenol by previous workers (Walker and Read, *J.*, 1934, 238; Cusmano and Boccucci, *Gazzetta*, 1923, **53**, 649) yielded mainly keto-alcohols, and no glycol appears to have been definitely isolated as a reaction product. Good yields of glycol have now been obtained by the hydrogenation in glacial acetic acid containing a trace of hydrogen chloride, when the reaction is carried out in the presence of Adams's platinum oxide catalyst at room temperature and a pressure of 30 atm. Fractionation of the product gave an appreciable amount of hydrocarbon and a glycol fraction which

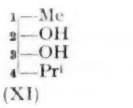
apparently contained only one diol. Crystallisation from light petroleum (b. p. 40—60°) gave the pure glycol, m. p. 76°, the di-*p*-nitrobenzoate of which melted at 147—148°. The same glycol was obtained from diosphenol by hydrogenation in ethanol solution at room temperature and 80 atm., Raney nickel (Pavlic and Adkins, *J. Amer. Chem. Soc.*, 1946, **68**, 1471) being used as catalyst. The glycol gave a monotoluene-*p*-sulphonate, m. p. 128°, which on reduction by lithium aluminium hydride (Schmid and Karrer, *Helv. Chim. Acta*, 1949, **32**, 1371) gave an oil possessing a strong menthol odour from which (±)-*neoiso*menthyl 3 : 5-dinitrobenzoate, m. p. 73°, was prepared. The *p*-nitrobenzoate could not be purified directly to a higher m. p. than 55°, a behaviour in accordance with Read and Grubb's observation (*J.*, 1934, 313).



(IX)



(X)



(XI)

The configuration of the glycol at $C_{(1)}$, $C_{(3)}$, and $C_{(4)}$ is fixed by its relationship with (±)-*neoiso*menthol (IX) and of the two possible configurations (X, XI) the latter [(±)-*cis*-2-hydroxy*neoiso*menthol] is preferred since the glycol did not appear as a product of the *trans*-hydroxylation of (±)-*cis*-menth-2-ene. The alternative configuration [(±)-*trans*-2-hydroxy*neoiso*menthol] has already been assigned to glycol D.

Although all the glycols examined readily yielded di-*p*-nitrobenzoates, only the (±)-*trans*-2-hydroxy*neo*menthol (m. p. 79°) gave a bis-3 : 5-dinitrobenzoate when esterified by normal methods. In the other cases the esters were obtained on heating the glycols under reflux for 30 min. with the acid chloride in benzene solution containing pyridine and leaving the mixture overnight. The esters were purified by crystallisation from benzene and light petroleum, and in some cases contained benzene of crystallisation. The bis-3 : 5-dinitrobenzoates of (±)-*cis*- and (±)-*trans*-2-hydroxy*neoiso*menthol contained two molecules of benzene of crystallisation which were readily lost at 80°. The ester of (±)-*trans*-2-hydroxymenthol contained one molecule of benzene which was released only on fusion, and glycol C, believed to be a 3 : 4-diol, behaved similarly.

Present views on the *p*-menthane-2 : 3-diols are summarised below.

Diol	M. p.	M. p. of di-*p*-nitrobenzoate	M. p. of bis-3 : 5-dinitrobenzoate
(±)-*cis*-2-Hydroxymenthol	—	163°	—
(±)-*trans*-2-Hydroxymenthol (B)	91°	118	218°
(±)-*cis*-2-Hydroxy*neo*menthol	—	—	—
(±)-*trans*-2-Hydroxy*neo*menthol (A)	79	168	173
(±)-*cis*-2-Hydroxy*iso*menthol	—	138	—
(±)-*trans*-2-Hydroxy*iso*menthol (E)	77	166	122
(±)-*cis*-2-Hydroxy*neoiso*menthol	76	147—148	82—83
(±)-*trans*-2-Hydroxy*neoiso*menthol (D)	69	152—153	65

The diosphenol initially used in the work was obtained by purification of a commercial sample of buchucamphor but, as the supply was limited, methods of preparing the substance were examined. Wallach (*Annalen*, 1924, **437**, 172) claimed to have obtained good yields of diosphenol by permanganate oxidation of piperitone, but subsequent workers (Düker, *J. pr. Chem.*, 1931, **129**, 145; Roberts, *J.*, 1915, **107**, 1466) did not find the method suitable, and in our hands yields of some 5% only were experienced. Nor did we find the oxidation of menthone by ferric chloride (Asahina and Mituhori, *J. Pharm. Soc. Japan*, 1922, **482**, 255; Asahina and Kuwada, *ibid.*, 1923, **491**, 1) or by selenium dioxide (Riley, Morley, and Friend, *J.*, 1932, 1875) satisfactory. Triebs and Bast's observation (*Annalen*, 1949, **561**, 165) that the action of meruric acetate on cyclic ketones gives rise to α-acetoxyketones, and in particular that 2-acetoxymenthone may be so derived, suggested that the oxidation of the 2-hydroxymenthone thus available might prove a suitable route to diosphenol. The use of bismuth oxide as a specific oxidising agent for acyloins to 1 : 2-diketones (Rigby, *J.*, 1951, 793) has proved satisfactory for the oxidation of 2-hydroxymenthone to diosphenol in yields approaching 50% on the menthone used.

Experimental

Diosphenol.—(*a*) A commercial sample of buchucamphor was distilled (b. p. 96—100°/10 mm.) and crystallised once from light petroleum (b. p. 40—60°). The purified diosphenol had m. p. 82°.

(*b*) *From menthone.* (−)-Menthone (15 g.) in glacial acetic acid (25 ml.) was heated with mercuric acetate (32 g.) at 130° until the crystalline mass which first formed had decomposed and precipitation of mercury was complete (2 hr.). Next morning the supernatant solution of 2-acetoxymenthone was decanted from the mercury and poured into water (400 ml.). After extraction with ether (150 ml.), drying ($MgSO_4$), and removal of the solvent by distillation, fractional distillation gave (i) unchanged menthone (3·5 g.), b. p. 55—60°/0·4 mm., and (ii) 2-acetoxymenthone (13·6 g., 77% on menthone used), b. p. 91—95°/0·4 mm. The 2-acetoxymenthone was obtained as a very pale yellow oil. A residue (0·8 g.) of viscid red oil remained after the distillation. 2-Acetoxymenthone (18 g.) was hydrolysed under reflux with a solution of potassium hydroxide (150 ml., 8%) for 20 min. The product was extracted with ether (100 ml.) and dried ($MgSO_4$), and the solvent removed by distillation. The residual 2-hydroxymenthone (12·2 g., 85%) was oxidised as follows without further purification.

2-Hydroxymenthone (12 g.) and bismuth oxide (15 g.) were heated in glacial acetic acid (40 ml.) at 110° for 2 hr. with constant agitation. After removal of the bismuth by filtration, the filtrate was poured into water (600 ml.). The product was extracted with ether (100 ml.) and the extract washed twice with aqueous sodium carbonate (5%, 50 ml., 50 ml.), then with water (50 ml.), and dried ($MgSO_4$). Removal of the solvent by distillation gave a residue which mostly crystallised but contained a small amount of yellow oil. Crystallisation of the residue from light petroleum (b. p. 40—60°) (cooled in the refrigerator) gave diosphenol (7·8 g., 73%), m. p. 82°. A mixture with an authentic sample (m. p. 82°) had m. p. 82°. The overall yield of diosphenol from menthone was 48%.

Reduction of Diosphenol with Sodium and Alcohol.—(*a*) Diosphenol (7 g.) was reduced in ethanol (125 ml.) with sodium (15 g.). After the addition of sodium was complete a further 50 ml. of ethanol was added, and the solution heated under reflux for 15 min. After cooling and dilution with water (200 ml.), ethanol was removed by distillation under partially reduced pressure. The product was continuously extracted (8 hr.) with light petroleum (b. p. 40—60°). No crystallisation from the petroleum solution (50 ml.) could be induced on cooling (finally to −80°). The solvent was removed by distillation, and the residue of crude glycol distilled under reduced pressure, yielding two fractions : (i) colourless oil (1·9 g.), b. p. 88—92°/1 mm., (ii) colourless viscid oil (4·3 g.), b. p. 118—120°/1 mm. Fraction (ii) partially crystallised. The crystals were separated from the oil by filtration and recrystallised from light petroleum, giving colourless needles (0·1 g.), m. p. 86—87°.

(*b*) Diosphenol (10 g.) was reduced with sodium (20 g.) in ethanol (200 ml.) as in (*a*). Fractionation of the crude product gave three fractions : (i) colourless oil with menthol odour (1·6 g.), b. p. 80—90°/0·8 mm., (ii) colourless, viscid oil (1·1 g.), b. p. 110—112°/0·8 mm., and (iii) colourless, very viscid oil (5·0 g.), b. p. 112—116°/0·8 mm.

Esterification of fraction (i) from (*b*) with *p*-nitrobenzoyl chloride (4 g.) in benzene (15 ml.) and pyridine (10 ml.) at room temperature for 24 hr. gave a crude ester (1·5 g.) from which was isolated by four recrystallisations from light petroleum (b. p. 40—60°) (±)-menthyl *p*-nitrobenzoate (0·25 g.), m. p. 91° (Found : C, 67·2; H, 7·5; N, 4·9. Calc. for $C_{17}H_{23}O_4N$: C, 66·9; H, 7·5; N, 4·6%). A mixture of this ester with an authentic sample of (±)-menthyl *p*-nitrobenzoate (m. p. 91°) melted at 91°.

Fraction (iii) from (*b*) partly crystallised slowly (several weeks) but was too viscous for filtration. Attempts to recrystallise the partly crystalline material from light petroleum (b. p. 40—60°) were unsuccessful. After removal of the solvent the remaining oil was combined with the remainder of fraction (ii) from (*a*) and refractionated, giving two fractions : (*a*) colourless, viscid oil (0·8 g.), b. p. 120—122°/7 mm., and (*b*) colourless, very viscid oil, b. p. 130—134°/7 mm. Fraction (*a*) was esterified with *p*-nitrobenzoyl chloride (2 g.) in benzene (15 ml.) and pyridine (15 ml.) at room temperature for 4 days. The product could not be crystallised satisfactorily. Crystallisation of fraction (*b*) from light petroleum (b. p. 40—60°) gave a crystalline glycol (1·5 g.), m. p. 86—88°. Two recrystallisations from light petroleum gave pure (±)-trans-2-*hydroxymenthol* (0·8 g.), m. p. 91° (Found : C, 70·0; H, 11·8. $C_{10}H_{20}O_2$ requires C, 69·8; H, 11·6%); the di-*p*-nitrobenzoate (Found : C, 61·7; H, 5·7; N, 6·2. Calc. for $C_{24}H_{26}O_8N_2$: C, 61·3; H, 5·5; N, 6·0%) had m. p. 118°, unchanged on admixture with a

sample of the di-*p*-nitrobenzoate (m. p. 118°) obtained from the product of hydroxylation of (±)-*trans*-menth-2-ene (Macbeth and Robertson, *loc. cit.*) with per-acetic acid.

(±)-trans-2-*Hydroxyisomenthol from the Sodium and Alcohol Reduction Product.*—The oil (4·7 g.) recovered from the mother-liquors accumulated during the purification of (±)-*trans*-2-hydroxymenthol was esterified with *p*-nitrobenzoyl chloride (13·8 g.) in pyridine (40 ml.) at room temperature for 4 days. The crude ester was obtained as a yellow oil (11·7 g.). Attempted crystallisation of the oil from methanol gave an oil. The mother-liquor slowly deposited pale yellow needles (0·52 g.), m. p. 160—162°. Crystallisation of the oil gave a further crop (0·96 g.), m. p. 158—162°. Further evaporation of the mother-liquor gave more crystalline material (2·47 g.), m. p. 155—160° with noticeable softening at 112—117°. Still further evaporation gave 2·6 g., m. p. 105—112° with marked softening at 85—90°. Attempts to isolate more crystalline material from the mother-liquors yielded only oils. Recrystallisation of the two fractions of higher m. p. from ethanol gave a di-*p*-nitrobenzoate (pale yellow needles), m. p. 166° (0·83 g.), identical with the di-*p*-nitrobenzoate of glycol E obtained from the hydroxylation of (±)-*cis*-menth-2-ene (Macbeth and Robertson, *loc. cit.*). This is now regarded as (±)-*trans*-2-hydroxy*iso*menthol.

(±)-*trans*-2-Hydroxy*iso*menthol di-*p*-nitrobenzoate (800 mg.) was hydrolysed under reflux for 2 hr. in methanol (12 ml.) containing potassium hydroxide (0·5 g.). After dilution with water (20 ml.) the methanol was removed by distillation. The glycol (200 mg.) crystallised from the aqueous liquor as fine colourless needles, m. p. 74—76°. One recrystallisation from light petroleum (b. p. <40°) gave pure (±)-*trans*-2-hydroxy*iso*menthol, m. p. 77°. Mixtures of the product with (±)-*cis*-2-hydroxy*neoiso*menthol (m. p. 76°), (±)-*trans*-2-hydroxy*neo*menthol (m. p. 79°), or glycol C (m. p. 78—78·5°) all melted within the range 35—45°. The m. p. was not depressed on admixture with the glycol E [(±)-*trans*-2-hydroxy*iso*menthol, m. p. 77°] obtained by per-acid hydroxylation of (±)-*cis*-menth-2-ene.

The two ester fractions of lower m. p. obtained from the crystallisation of the crude di-*p*-nitrobenzoate probably consisted of mixtures of (±)-menthyl *p*-nitrobenzoate and the di-*p*-nitrobenzoates of (±)-*trans*-2-hydroxymenthol and of (±)-*trans*-2-hydroxy*iso*menthol and could not be purified satisfactorily by recrystallisation.

Hydrogenation of Diosphenol over Raney Nickel.—Diosphenol (7 g.) was suspended in ethanol (10 ml.) and hydrogenated during 2·5 hr. at room temperature 1200 lb./sq. in over Raney nickel. (0·5 g.). The hydrogenated solution was filtered and diluted with water (25 ml.). The alcohol was removed by distillation, and the product extracted continuously from the residue for 4 hr. with light petroleum (b. p. 40—60°). The extract was reddish. The petroleum extract was concentrated to 15 ml. The glycol crystallised from the solvent during 2 days at room temperature. The crystalline glycol obtained (2·1 g.) had m. p. 75—76°. On further evaporation the mother-liquor yielded an additional quantity of glycol (1·5 g.), m. p. 68—72°. Recrystallisation of this second crop gave 0·9 g., m. p. 75—76°. Recrystallisation of all the glycol, m. p. 75—76° (3·0 g.), gave pure (±)-cis-2-*hydroxy*neoiso*menthol* as needles (from light petroleum) (2·0 g.), m. p. 76° (Found : C, 69·8; H, 11·4. $C_{10}H_{20}O_2$ requires C, 69·8; H, 11·6%); *di-p-nitrobenzoate*, m. p. 148° (Found : C, 61·5; H, 5·8; N, 6·0. $C_{24}H_{26}O_8N_2$ requires C, 61·3; H, 5·5; N, 6·0%). Admixture with (±)-*trans*-2-hydroxy*neo*menthol (m. p. 79°) and with (±)-*trans*-2-hydroxy*iso*menthol (m. p. 77°) depressed the m. p. to 30—40° and to 45—50°, respectively. The di-*p*-nitrobenzoate (m. p. 148°) of (±)-*cis*-2-hydroxy*neoiso*menthol when admixed with the di-*p*-nitrobenzoate (m. p. 152—153°) of (±)-*trans*-2-hydroxy*neoiso*menthol melted at 135—140°.

Hydrogenation of Diosphenol over Adams's Catalyst.—Diosphenol (10 g.) was suspended in glacial acetic acid (30 ml.). After the addition of concentrated hydrochloric acid (1 drop) the mixture was hydrogenated over platinum oxide (200 mg.) during 1 hr. at 25°/400 lb./sq. in. The solution was filtered and poured into water (500 ml.). The product was extracted with ether (100 ml.), and the ethereal solution washed with water (100 ml.), 5% sodium carbonate solution (100 ml.), and again with water (100 ml.). After drying ($MgSO_4$), the solvent was removed from the extract by distillation. Crystallisation of the colourless residue (8·6 g.) from light petroleum (b. p. 40—60°) gave (±)-*cis*-2-hydroxy*neoiso*menthol (4·5 g.), m. p. 75—76°. One recrystallisation from light petroleum raised the m. p. to 76°. The product was identical with that obtained by hydrogenation of diosphenol over Raney nickel and gave the same di-*p*-nitrobenzoate, m. p. 147—148°.

Careful fractionation of the material recovered from the mother-liquors from the purification of the glycol from several such preparations gave a large range of fractions whose b. p.s ranged from 58°/1 mm. to 95°/1 mm. Their compositions were not determined. A glycol fraction,

b.p. 98—100°, amounting to 15% of the total material (14·2 g.) fractionated, was obtained. From this only (±)-*cis*-2-hydroxy*neoiso*menthol (m. p. 76°) could be obtained by crystallisation from light petroleum (b. p. 40—60°).

Monotoluene-p-*sulphonate of* (±)-cis-2-*Hydroxy*neoiso*menthol*.—(±)-*cis*-2-Hydroxy*neoiso*menthol (0·86 g.) was esterified with toluene-*p*-sulphonyl chloride (2·5 g.) in pyridine (7 ml.) during 24 hr. at room temperature. Crystallisation of the crude product from aqueous methanol gave colourless leaflets, m. p. 126—127°. Recrystallisation from aqueous methanol gave the pure *monotoluene*-p-*sulphonate*, m. p. 128° (Found : C, 62·6; H, 7·9; S, 9·7. $C_{17}H_{26}O_4S$ requires C, 62·6; H, 8·0; S, 9·8%).

(±)-neoiso*Menthol*.—The monotoluene-*p*-sulphonate (400 mg.) was heated under reflux with lithium aluminium hydride (30 mg.) in dry ether during 24 hr. The excess of lithium aluminium hydride was decomposed with water, and the white precipitate dissolved by addition of 2N-sulphuric acid. After being washed with 2N-sodium hydroxide (15 ml.) and water (15 ml.), the ethereal solution was dried ($MgSO_4$) and the solvent removed, leaving a colourless oil (200 mg.). Esterification as above gave (±)-*neoiso*menthyl *p*-nitrobenzoate (yellow leaflets from light petroleum), m. p. 55—56°. Esterification with 3 : 5-dinitrobenzoyl chloride gave (±)-*neoiso*menthyl 3 : 5-dinitrobenzoate, m. p. 73°.

Bis-3 : 5-*dinitrobenzoates*.—(*a*) (±)-*trans*-2-Hydroxy*neo*menthol (200 mg.) was esterified with 3 : 5-dinitrobenzoyl chloride in pyridine in the usual way. Crystallisation of the crude ester from ethanol gave (±)-trans-2-*hydroxy*neo*menthol bis*-3 : 5-*dinitrobenzoate* as small, pale yellow rosettes, m. p. 173° (Found : C, 51·7; H, 4·5; N, 10·0. $C_{24}H_{24}O_{12}N_4$ requires C, 51·4; H, 4·3; N, 10·0%).

(*b*) In all other cases the bis-3 : 5-dinitrobenzoates were prepared by boiling the glycol (100—200 mg.) and 3 : 5-dinitrobenzoyl chloride (300—600 mg.) under reflux in benzene (12 ml.) and pyridine (3 ml.) for 0·5 hr. and keeping the mixture at room temperature overnight. The crude esters were crystallised from mixtures of benzene and light petroleum, with the following results :

(i) (±)-*trans*-2-Hydroxymenthol (m. p. 91°) gave the corresponding *bis*-3 : 5-*dinitrobenzoate* as pale yellow needles, m. p. 218°, containing 1 molecule of benzene of crystallisation (Found : C, 55·5; H, 4·5; N, 8·8. $C_{24}H_{24}O_{12}N_4,C_6H_6$ requires C, 55·6; H, 4·6; N, 8·8%). The benzene of crystallisation could be removed only by fusion of the ester (Found, for unsolvated *ester* : C, 51·5; H, 4·3; N, 10·3. $C_{24}H_{24}O_{12}N_4$ requires C, 51·4; H, 4·3; N, 10·0%).

(ii) (±)-*trans*-2-Hydroxy*iso*menthol (m. p. 77°) gave the corresponding *bis*-3 : 5-*dinitrobenzoate* as pale yellow, unsolvated needles, m. p. 122°, containing no benzene of crystallisation (Found : C, 51·5; H, 4·3; N, 10·0%).

(iii) (±)-*trans*-2-Hydroxy*neoiso*menthol (m. p. 69°) gave a *bis*-3 : 5-*dinitrobenzoate* as pale yellow, transparent leaflets, m. p. 65°, containing two molecules of benzene of crystallisation. Heating the freshly crystallised ester (61·8 mg.) for 2 hr. at 100° under reduced pressure (0·1 mm.) caused a loss in weight of 21·7% (13·4 mg.) ($C_{24}H_{24}O_{12}N_4,2C_6H_6$ requires $2C_6H_6$, 21·8%). The residue (48·4 mg.) of desolvated *ester* was obtained as a glass with an indefinite m. p. 70—75° (Found : C, 51·8; H, 4·3; N, 9·8%). When kept for several days the freshly crystallised ester lost one molecule of benzene, the *monosolvate* having an opaque powdery appearance (Found : C, 55·7; H, 4·5; N, 8·8%).

(iv) Glycol C (m. p. 78—78·5°) gave a monosolvated *bis*-3 : 5-*dinitrobenzoate* as pale yellow needles, m. p. 185° (Found : C, 55·9; H, 4·6; N, 9·2%). The benzene of crystallisation could be removed only by fusion of the ester for several minutes (Found, for unsolvated *ester* : C, 51·6; H, 4·5; N, 9·9%).

(v) (±)-*cis*-2-Hydroxy*neoiso*menthol gave a disolvated *bis*-3 : 5-*dinitrobenzoate* as pale yellow prisms, m. p. 81—83° (Found : C, 60·6; H, 5·1; N, 7·5. $C_{36}H_{36}O_{12}N_4$ requires C, 60·5; H, 5·0; N, 7·8%). A small sample (101·2 mg.) of the ester heated under reduced pressure (0·1 mm.) for 2 hr. at 80° and a further 1 hr. at 110° underwent a loss in weight of 21·4% (21·6 mg.) ($2C_6H_6$ requires 21·8%) giving the pure *ester*, m. p. 169° (Found : C, 51·7; H, 4·5; N, 9·9%).

(vi) Attempts to prepare bis-3 : 5-dinitrobenzoates from (±)-*cis*-2-hydroxymenthol and from (±)-*cis*-2-hydroxy*iso*menthol failed.

JOHNSON CHEMICAL LABORATORIES,
THE UNIVERSITY OF ADELAIDE.

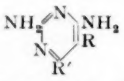
[*Received, June 20th*, 1953.]

707. *The Preparation of Enol Ethers from Certain β-Keto-nitriles.*

By B. H. Chase and James Walker.

αβ-Unsaturated β-alkoxy-nitriles, the enol ethers of β-keto-nitriles, are intermediates in the synthesis of highly active antimalarials of the 2 : 4-diaminopyrimidine type. Methods for the preparation of such enol ethers are reviewed, and the acid-catalysed etherification of β-keto-nitriles has been studied in detail. Infra-red absorption characteristics of β-keto-nitriles are discussed.

The production of antimalarials of the 2 : 4-diaminopyrimidine type (I), such as the highly active pyrimethamine (2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine) (II), calls for accessibility of the αβ-unsaturated β-alkoxy-nitriles (III; R″ = alkyl), which are intermediates yielding (I) on condensation with guanidine (Russell and Hitchings, *J. Amer. Chem. Soc.*, 1951, **73**, 3763; Chase, Thurston, and Walker, *J.*, 1951, 3439). These unsaturated nitriles (III) are, of course, enol ethers of the corresponding β-keto-(or β-aldehydo-, when R′ = H) nitriles (IV), and the latter are relatively easy of access by Claisen condensation of esters (*e.g.*, R′·CO_2Et) with appropriate nitriles (R·CH_2·CN), although they (IV) do not themselves react with guanidine to give diaminopyrimidines but yield aminotriazines instead (Russell, Hitchings, Chase, and Walker, *J. Amer. Chem. Soc.*, 1952, **74**, 5403).

(I) 

(V)

(II; R = *p*-Cl·C_6H_4, R′ = Et)
(VI; R = H, R′ = *p*-Cl·C_6H_4)
(VII; R = R′ = *p*-Cl·C_6H_4)

(III) R′·C(OR″):CR·CN

(IV*a*) R′·CO·CHR·CN ⟷ R′·C(OH):CR·CN (IV*b*)

Whether alkylation of such β-keto-nitriles (IV) by hitherto conventional methods affords *O*- or *C*-alkylated derivatives obviously depends upon structural factors as well as upon the choice of reagents and conditions of reaction. In the case of 1-cyanoindan-2-one, for example, *O*-methylation takes place with methyl sulphate and *C*-methylation occurs exclusively with sodium methoxide and methyl iodide, yet *O*-ethylation occurs with sodium ethoxide and ethyl iodide (Moore and Thorpe, *J.*, 1908, **93**, 165). By contrast, however, 2-cyanoindan-1-one undergoes exclusive *O*-methylation with sodium methoxide and methyl iodide (Mitchell and Thorpe, *J.*, 1910, **97**, 2278). The sodium salt of 2-cyano*cyclo*hexanone undergoes mainly *C*- but also *O*-alkylation with alkyl halides (von Auwers, *Ber.*, 1928, **61**, 408), and that of 2-cyano*cyclo*pentanone undergoes exclusive *C*-methylation and -ethylation (Best and Thorpe, *J.*, 1909, **95**, 711), yet with 3-cyanocamphor (V) *O*-alkylation apparently predominates over *C*-alkylation under comparable conditions (Haller and Minguin, *Compt. rend.*, 1894, **118**, 690; Haller, *ibid.*, 1903, **136**, 788). Exclusive *O*-methylation, either with methyl sulphate and aqueous potassium hydroxide or with methyl iodide and silver oxide, of α-cyanoacetomesitylene (IV; R = H, R′ = mesityl) has been reported (Fuson, Ullyot, and Gehrt, *J. Amer. Chem. Soc.*, 1938, **60**, 1199) though *O*- and *C*-methylation occur to roughly equal extents with methyl iodide and sodium ethoxide (Fuson and Wolf, *ibid.*, 1939, **61**, 1940), while *p*-bromo-ω-cyanoacetophenone (IV; R = H, R′ = *p*-Br·C_6H_4) afforded the *O*-methyl ether with the first of these reagents and the *C*-methylated compound with the last (Fuson and Wolf, *loc. cit.*). Methyl sulphate and aqueous potassium hydroxide convert cyanodeoxybenzoin (IV; R = R′ = Ph) into stereoisomeric enol methyl ethers (Reynaud and Matti, *Compt. rend.*, 1952, **235**, 1231) but the conditions for reaction appear to be hard to define and the method lacks general usefulness (Russell and Whittaker, *J. Amer. Chem. Soc.*, 1952, **74**, 1310).

The necessity for ensuring *O*-alkylation led to the use of diazomethane for the methylation of β-keto-nitriles (IV) (Russell and Hitchings, *loc. cit.*; Chase, Thurston, and Walker, *loc. cit.*) but more satisfactory results in the case of α-formylphenylacetonitrile (IV; R = Ph,

R′ = H) were obtained on methylation with methyl iodide and potassium carbonate (Chase, Thurston, and Walker, *loc. cit.*). Reaction between β-keto-nitriles and aliphatic ortho-esters also leads to *O*-alkylation but with orthoformic ester displacement of the acyl group, R′·CO, may occur with production of an ethoxymethyleneacetonitrile (Russell and Whittaker, *loc. cit.*), and the method is not applicable to β-keto-nitriles (IV; R = H) containing a methylene group activated by two strongly negative groups (Pascual and Serratosa, *Chem. Ber.*, 1952, **85**, 686; cf. Russell and Whittaker, *loc. cit.*). We have previously reported (Chase, Thurston, and Walker, *loc. cit.*) that α-formylphenylacetonitrile (IV; R = Ph, R′ = H) and its *p*-chloro-analogue (IV; R = *p*-Cl·C_6H_4, R′ = H) may be conveniently converted into their *O-iso*butyl derivatives (III; R = Ph, R′ = H, R″ = Bu^i and R = *p*-Cl·C_6H_4, R′ = H, R″ = Bu^i) by treatment with *iso*butanol and an acid catalyst in a boiling inert solvent capable of forming a heterogeneous azeotropic mixture with water in such a manner that water is removed from the reaction mixture as it is formed. The present communication extends these observations and shows that, besides β-aldehydo-nitriles, β-keto-nitriles come within the scope of the method subject to certain reservations which will be discussed later. This general technique has been applied to dihydroresorcinols but it fails with dihydro-2-methylresorcinols (Frank and Hall, *J. Amer. Chem. Soc.*, 1950, **72**, 1645; Meek, Turnbull, and Wilson, *J.*, 1953, 811), and it is applicable to hydroxymethylene-ketones (Seifert and Schinz, *Helv. Chim. Acta*, 1951, **34**, 728). There was no *a priori* reason, however, to believe that this method would be outstandingly successful with β-keto-nitriles without interference from the cyano-group, since imidic ester salt formation could occur with inactivation of the acid catalyst, and it may be noted that β-keto-nitriles of this type (*e.g.*, IV; R = Ph, R′ = Pr^i) may actually be converted into β-keto-esters *via* the imidic esters (Wislicenus, Eichert, and Marquardt, *Annalen*, 1924, **436**, 88). With regard to the conditions of the reaction, the solvent employed should be one forming a heterogeneous azeotropic mixture with water having a boiling point lower than that of the alcohol being used; a solvent forming a ternary azeotrope with water and the alcohol may also be used provided enough alcohol is present in the reaction vessel throughout. The presence of too great an excess of the alcohol is perhaps to be avoided since acetals may be formed, as in the case of α-formylphenylacetonitrile (IV; R = Ph, R′ = H) (cf. the preparation of dimethyl β-keto-acetals and methoxymethylene ketones from hydroxymethylene-ketones; Royals and Brannock, *J. Amer. Chem. Soc.*, 1953, **75**, 2050). The acetals, *e.g.*, ββ-di*iso*butoxy-α-phenylpropionitrile, $CH(OBu^i)_2$·CHPh·CN, are, however, readily converted into enol ethers (III) on treatment with acid as described below. Either primary or secondary alcohols may be employed, although benzyl alcohol is an exception, and phenol was tried unsuccessfully. Sulphonic acids are convenient catalysts for the etherification, and "Zeo-Karb 225," a sulphonated polystyrene, is also effective, the present reaction being an addition to the growing number of types of reaction now known to be catalysed by cation-exchange resins.

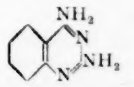
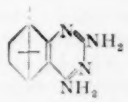
Turning now to the β-keto-nitriles it is obvious that these (IV*a*) are in tautomeric equilibrium with the enolic forms (IV*b*), and the latter are presumably the forms participating in the reaction in a similar manner to the esterification of carboxylic acids. It might be expected, therefore, that the rate of acid-catalysed etherification would be related to the degree of enolisation of any particular β-keto-nitrile modified, of course, by steric factors influencing the accessibility of the β-carbon atom and by the mobility of the tautomeric equilibrium. Evidence as to the structure of a β-keto-nitrile under the conditions of the etherification reaction is not easily obtained but it may be noted that ω-cyanoacetophenone (IV; R = H, R′ = Ph) in alcoholic solution appears to exist to the extent of ~10% as the enolic form while α-phenylacetoacetonitrile (IV; R = Ph, R′ = Me) is ~90% enolised under the same conditions as shown by bromine titration (Arndt, Loewe, and Ginkök, *Rev. Fac. Sci. Istanbul*, 1946, *A*, **11**, 147), and 2-cyano*cyclo*hexanone is similarly shown to be ~10% enolised (von Auwers, Bahr, and Frese, *Annalen*, 1925, **441**, 68). We have studied the infra-red absorption in Nujol suspension of a range of the β-keto-nitriles (IV) used in the present work and find that the results are in general accord with other available collateral data. Thus, α-formylphenylacetonitrile (IV; R = Ph, R′ = H) shows a band at 3040 cm.$^{-1}$ due to the enolic hydroxyl

group and a band at 1635 cm.$^{-1}$ due to the conjugated double bond, the latter being approximately in the same position as, and comparable in intensity with, the band at ~1640 cm.$^{-1}$ observed for αβ-unsaturated nitriles (Barnes, Liddel, and Williams, *Ind. Eng. Chem. Anal.*, 1943, **15**, 699). Likewise, α-phenylacetoacetonitrile (IV; R = Ph, R′ = Me) shows bands at 3070 and 1660 cm.$^{-1}$, α-*p*-chlorophenyl-α-propionylacetonitrile (IV; R = *p*-Cl·C_6H_4, R′ = Et) shows bands at 3050 and 1615 cm.$^{-1}$, and cyanodeoxybenzoin (IV; R = R′ = Ph) shows bands at 3090 and 1610 cm.$^{-1}$. These substances therefore exist in the solid essentially in the enolic form, and, as pointed out above, the enolic form of α-phenylacetoacetonitrile (IV; R = Ph, R′ = Me) also predominates in alcoholic solution (Arndt, Loewe, and Ginkök, *loc. cit.*), while ultra-violet light absorption also indicates predominantly the enolic structure for cyanodeoxybenzoin (Russell, *J. Amer. Chem. Soc.*, 1952, **74**, 2654). With ω-cyanoacetophenone (IV; R = H, R′ = Ph) and *p*-chloro-ω-cyanoacetophenone (IV; R = H, R′ = *p*-Cl·C_6H_4) no absorption band is found in the 3000—3500-cm.$^{-1}$ region and absorption bands ascribable to carbonyl groups linked to the benzene ring are found at 1685 and 1680 cm.$^{-1}$ respectively in Nujol (or at 1690 cm.$^{-1}$ in chloroform solution). Both in the solid and in chloroform solution therefore these substances are essentially ketonic, as has been shown also for the former in alcoholic solution (Arndt, Loewe, and Ginkök, *loc. cit.*). 3-Cyanocamphor (V) shows a band at 1735 cm.$^{-1}$ due to the alicyclic carbonyl group, and, by way of analogy, camphorcarboxylic ester is also ketonic, existing to the extent of only 0·1% in the enolic form in alcoholic solution (Henecka, *Chem. Ber.*, 1948, **81**, 204). Ethyl β-cyano-β-phenylpyruvate was also examined and found to show bands at ~3130, 2200, 1720, and 1625 cm.$^{-1}$, which are attributed to the enolic hydroxyl group, the nitrile group, the ester carbonyl group, and the conjugated double bond respectively. Throughout the series of β-keto-nitriles (IV) and enol ethers (III) studied, weak to medium intensity but well-defined sharp bands due to the nitrile group appeared at 2200—2240 cm.$^{-1}$.

No strict correlation between these structures and ease of acid-catalysed etherification was discernible. The following order of decreasing ease of reaction was, however, observed: α-formylphenylacetonitrile (IV; R = Ph, R′ = H), *p*-chloro-α-formylphenylacetonitrile (IV; R = *p*-Cl·C_6H_4, R′ = H), α-phenylacetoacetonitrile (IV; R = Ph, R′ = Me), *p*-chloro-ω-cyanoacetophenone (IV; R = H, R′ = *p*-Cl·C_6H_4), α-*p*-chlorophenyl-α-propionylacetonitrile (IV; R = *p*-Cl·C_6H_4, R′ = Et); 4 : 4′-dichlorocyanodeoxybenzoin (IV; R = R′ = *p*-Cl·C_6H_4) and cyanocamphor (V) failed to react while ethyl β-cyano-β-phenylpyruvate, CHPh(CN)·CO·CO_2Et, underwent dismutation. The failure of 4 : 4′-dichlorocyanodeoxybenzoin to react may be due to steric hindrance coupled with a clearly discernible retarding effect of *p*-chloro-substituents, but the unreactivity of cyanocamphor is less easily understandable since it reacted comparatively readily with diazomethane as, of course, did 4 : 4′-dichlorocyanodeoxybenzoin; in contrast with cyanocamphor, 2-cyano*cyclo*hexanone underwent acid-catalysed etherification with relative ease. One may conclude, therefore, that the acid-catalysed etherification reaction is shown by the enolic modifications (IV*b*) of the β-keto-nitriles (IV*a*), provided steric hindrance does not interfere, and that essentially ketonic substances will also undergo the reaction provided the mobility of the tautomeric equilibrium is adequate. That reaction does not take place through the intermediary of alkyl sulphonates was shown by recovery of α-formylphenylacetonitrile (IV; R = Ph, R′ = H) from attempted reaction with *iso*butyl toluene-*p*-sulphonate.

2 : 4-Diamino-6-methyl-5-phenylpyrimidine (I; R = Ph, R′ = Me) and pyrimethamine (II) were obtained in about 90% yield by condensation of β-*iso*butoxy-α-phenylcrotononitrile (III; R = Ph, R′ = Me, R″ = Bu^i) and 3-*iso*butoxy-2-*p*-chlorophenylpent-2-enonitrile (III; R = *p*-Cl·C_6H_4, R′ = Et, R″ = Bu^i) respectively with guanidine. β-*iso*Butoxy-β-*p*-chlorophenylacrylonitrile (III; R = H, R′ = *p*-Cl·C_6H_4, R″ = Bu^i) and αβ-bis-*p*-chlorophenyl-β-methoxyacrylonitrile (III; R = R′ = *p*-Cl·C_6H_4, R″ = Me), however, afforded 2 : 4-diamino-6-*p*-chlorophenylpyrimidine (VI) and 2 : 4-diamino-5 : 6-bis-*p*-chlorophenylpyrimidine (VII) respectively in moderate yield. By contrast, drastic conditions were necessary for the condensations of 1-*iso*butoxy-2-cyano*cyclo*hexene and 3-cyano-2-methoxycamph-2-ene with guanidine and poor yields of 2 : 4-diamino-5 : 6 : 7 : 8-

tetrahydroquinazoline (VIII) and 2 : 6-diaminocamph-2′-eno(2′ : 3′-4 : 5)pyrimidine (IX) * respectively resulted.

(VIII)   (IX)

The above substituted pyrimidines (I; R = Ph, R′ = Me), (VI), (VII), (VIII), and (IX) were kindly tested for antimalarial activity by Dr. June Thurston. Only the first of them showed activity, being active at 2 mg./20 g. mouse given intraperitoneally b.i.d. × 4 in the mouse against *P. berghei* and at 2 mg./10 g. chick given orally b.i.d. × 3½ in the chick against *P. gallinaceum* (cf. Falco, Goodwin, Hitchings, Rollo, and Russell, *Brit. J. Pharmacol.*, 1951, **6**, 187); none of the others showed observable activity against *P. berghei* in the mouse under the usual conditions of testing, and (VI) and (VII) were also inactive against *P. gallinaceum* in the chick.

Experimental

Infra-red absorption spectra were recorded between 700 and 4000 cm^{-1}; only significant absorption bands found in the 1600—4000 $cm.^{-1}$ region are reported in this communication.

β-Ethoxy-α-phenylacrylonitrile (III; R = Ph, R′ = H, R″ = Et).—A mixture of α-formylphenylacetonitrile (Ghosh, *J.*, 1916, **109**, 113) (14·5 g.), ethanol (6·9 g., 50% excess), and (+)-camphor-10-sulphonic acid (2·32 g.) in dry chloroform (200 c.c.) was refluxed for 42 hr., the condensate passing through an automatic separator allowing only the heavier, chloroform layer to return to the reaction vessel. The cooled solution was washed with N-sodium hydroxide and with water, and then fractionated, yielding a mixture (12·3 g.), b. p. 107—115°/0·4 mm., n_D^{17} 1·5194—1·5668, of the enol ether and the acetal. Redistillation after the addition of 1 drop of concentrated sulphuric acid gave *β-ethoxy-α-phenylacrylonitrile* as a colourless oil (10·2 g.), b. p. 116—118°/0·4 mm., n_D^{22} 1·5676, absorption bands (homogeneous) at 1620 and 2200 $cm.^{-1}$ (Found: C, 76·2; H, 6·4; N, 8·4. $C_{11}H_{11}ON$ requires C, 76·3; H, 6·4; N, 8·1%).

α-Phenyl-β-n-propoxyacrylonitrile (III; R = Ph, R′ = H, R″ = Pr^n).—A suspension of activated (*i.e.*, acid-treated) "Zeo-Karb 225" in a benzene solution (200 c.c.) of α-formylphenylacetonitrile (14·5 g.) containing *n*-propanol (6·6 g., 10% excess) was refluxed for 7 hr., the condensate being returned to the reaction vessel *via* a conventional Dean and Stark separator. The mixture was cooled, filtered, and washed with N-sodium hydroxide, unchanged formylphenylacetonitrile (1·05 g., 7·2%) being recovered by acidification of the alkaline washings. Fractionation of the benzene layer then afforded *α-phenyl-β-n-propoxyacrylonitrile* (15·4 g., 82%), b. p. 120—122°/0·4 mm., n_D^{19} 1·5598 (Found: C, 77·1; H, 6·9. $C_{12}H_{13}ON$ requires C, 77·0; H, 7·0%). In a similar experiment employing toluene-*p*-sulphonic acid (4·0 g.) in place of "Zeo-Karb 225" the same product was obtained in 88% yield after a 16-hr. period of reflux.

α-Phenyl-β-isopropoxyacrylonitrile (III; R = Ph, R′ = H, R″ = Pr^i).—A mixture of α-formylphenylacetonitrile (7·25 g.), *iso*propanol (3·3 g.), toluene-*p*-sulphonic acid (0·98 g.) and dry benzene (100 c.c.) was boiled under reflux in the manner described above for 5 hr. The neutral fraction was distilled and *α-phenyl-β-isopropoxyacrylonitrile* passed over at 123—124°/0·4 mm. as a colourless oil (8·17 g., 87%), n_D^{18} 1·5578 (Found: C, 76·7; H, 6·8; N, 7·6%).

β-isoButoxy-α-phenylacrylonitrile (III; R = Ph, R′ = H, R″ = Bu^i).—(*a*) The following procedure is more convenient than that previously described (Chase, Thurston, and Walker, *loc. cit.*). A mixture of α-formylphenylacetonitrile (96 g.), *iso*butanol (58 g.), toluene-*p*-sulphonic acid (10 g.), and toluene (450 c.c.) was boiled under reflux as in the preceding experiment for 2 hr., during which the theoretical volume of water was segregated. The cooled solution was washed with N-sodium hydroxide and fractionated, *β-iso*butoxy-α-phenylacrylonitrile (114 g., 85%) passing over at 124—127°/0·4 mm., n_D^{22} 1·5475.

(*b*) A mixture of α-formylphenylacetonitrile (50 g.), *iso*butanol (60 g.), toluene-*p*-sulphonic acid (1 g.), and benzene (600 c.c.) was refluxed as above for 22 hr. The mixture, worked up as before, gave *α-cyanophenylacetaldehyde diisobutyl acetal* (56 g.), b. p. 115—118°/0·03 mm., n_D^{20} 1·4948 (Found: C, 74·4; H, 8·8. $C_{17}H_{25}O_2N$ requires C, 74·2; H, 9·2%). The acetal (122 g.)

* In the name for (IX) camphene is used systematically for a monounsaturated derivative of camphane. The naturally occurring, trivially named camphene is, of course, a derivative of *iso*camphane.—Ed.

was heated on the water-bath with toluene-*p*-sulphonic acid (10 g.) under slightly reduced pressure, *iso*butanol distilling over as it was formed. The residue, in ether, was washed with N-sodium hydroxide and water, dried, and fractionated, affording β-*iso*butoxy-α-phenylacrylonitrile (75 g.), n_D^{20} 1·5468, distilling at 116—118°/0·03 mm.

β-cyclo*Hexyloxy-α-phenylacrylonitrile* (III; R = Ph, R′ = H, R″ = C_6H_{11}).—A mixture of α-formylphenylacetonitrile (7·25 g.), *cyclo*hexanol (6·0 g.), toluene-*p*-sulphonic acid (0·9 g.), and dry toluene (100 c.c.) was boiled under reflux as above for 1 hr. The neutral fraction was distilled and β-cyclo*hexyloxy-α-phenylacrylonitrile* (10·44 g., 92%) passed over at 140—142°/0·004 mm., n_D^{18} 1·5718 (Found: C, 79·2; H, 7·4; N, 6·3. $C_{15}H_{17}ON$ requires C, 79·3; H, 7·5; N, 6·2%).

β-*Dodecyloxy-α-phenylacrylonitrile* (III; R = Ph, R′ = H, R″ = $C_{12}H_{25}$).—Similarly, α-formylphenylacetonitrile (7·25 g.), dodecanol (10·25 g.) toluene-*p*-sulphonic acid (0·9 g.), and toluene (100 c.c.), refluxed for 2 hr., afforded β-*dodecyloxy-α-phenylacrylonitrile* (15·1 g., 96%) as a pale yellow oil, b. p. 185—190°/0·002 mm., n_D^{22} 1·5206 (Found: C, 80·2; H, 9·8; N, 4·7. $C_{21}H_{31}ON$ requires C, 80·4; H, 10·0; N, 4·5%).

Enol-etherification using (a) *Internal and* (b) *External Drying Agents.*—(*a*) A mixture of α-formylphenylacetonitrile (7·25 g.), *n*-propanol (3·6 g.), toluene-*p*-sulphonic acid (0·9 g.), anhydrous calcium sulphate (41 g.), and benzene (150 c.c.) was boiled under reflux with vigorous stirring for 9 hr. The filtered solution, treated in the usual way, gave a neutral fraction which yielded, on distillation in the presence of 1 drop of concentrated sulphuric acid, α-phenyl-β-*n*-propoxyacrylonitrile (4·5 g., 48%), b. p. 120—124°/0·15 mm., n_D^{21} 1·5592.

(*b*) A mixture of α-formylphenylacetonitrile (7·25 g.), *iso*butanol (4·1 g.), toluene-*p*-sulphonic acid (0·9 g.) and dry benzene (150 c.c.) was boiled under reflux in such a way that the condensate passed over anhydrous calcium chloride (50 g.) before returning to the reaction mixture. After 6 hr. at the b. p. the mixture was worked up in the usual way, giving β-*iso*butoxy-α-phenylacrylonitrile (9·6 g., 95%), b. p. 112—114°/0·005 mm., n_D^{18} 1·5492.

Attempted Preparation of β-iso*Butoxy-α-phenylacrylonitrile using* iso*Butyl Toluene*-p-*sulphonate.*—A mixture of α-formylphenylacetonitrile (14·5 g.), *iso*butyl toluene-*p*-sulphonate (11·4 g.), prepared by the general method of Marvel and Sekera (*Org. Synth.*, **20**, 50), and benzene (100 c.c.) was boiled under reflux in the usual way, the Dean and Stark separator being used, for 3 hr. The starting materials were recovered.

β-iso*Butoxy-α-phenylcrotononitrile* (III; R = Ph, R′ = Me, R″ = Bu^i).—A mixture of α-phenylacetoacetonitrile (50 g.) (*Org. Synth.*, Coll. Vol. II, 487), *iso*butanol (50 g.), toluene-*p*-sulphonic acid (1·0 g.), and benzene was boiled under reflux for 72 hr., the Dean and Stark apparatus being used. The neutral fraction, isolated in the usual way, yielded, on distillation, β-iso*butoxy-α-phenylcrotononitrile* as an almost colourless oil (65 g., 96%), b.p. 118—120°/0·005 mm., n_D^{19} 1·5514 (Found: C, 78·1; H, 8·0; N, 6·5. $C_{14}H_{17}ON$ requires C, 78·1; H, 7·9; N, 6·5%).

3-iso*Butoxy*-2-p-*chlorophenylpent-2-enonitrile* (III; R = *p*-Cl·C_6H_4, R′ = Et, R″ = Bu^i).—A mixture of α-*p*-chlorophenyl-α-propionylacetonitrile (5·2 g.) (Russell and Hitchings, *loc. cit.*), *iso*butanol (2·05 g., 10% excess), toluene-*p*-sulphonic acid (0·5 g.), and toluene (100 c.c.) was boiled under reflux as above for 44 hr., during which the calculated volume of water was segregated. The neutral fraction, isolated in the usual way, gave, on distillation, 3-iso*butoxy*-2-p-*chlorophenylpent-2-enonitrile* (4·62 g., 70%), b. p. 140—141°/0·2 mm., n_D^{20} 1·5587, absorption bands (homogeneous) at 1600(s), 2210(m), 2850(w), and 2935(m) cm.$^{-1}$ (Found: C, 68·3; H, 6·8; N, 5·6. $C_{15}H_{16}ONCl$ requires C, 68·3; H, 6·9; N, 5·3%).

When an attempt was made to prepare the analogous *cyclo*hexyl ether, 82% of unchanged keto-nitrile was recovered after a 24-hr. period of reflux.

β-iso*Butoxy*-β-p-*chlorophenylacrylonitrile* (III; R = H, R′ = *p*-Cl·C_6H_4, R″ = Bu^i).—Bromination of *p*-chloroacetophenone in glacial acetic acid below 20° (cf. *Org. Synth.*, Coll. Vol. I, 1st Edn., p. 122) and treatment of the air-dried *p*-chlorophenacyl bromide with sodium cyanide in aqueous ethanol below 20° (cf. Long, *J. Amer. Chem. Soc.*, 1947, **69**, 990) gave *p*-chlorobenzoylacetonitrile, m. p. 125—126°, in 61% overall yield. Recrystallisation from aqueous ethanol afforded lustrous needles, m. p. 129—131°, absorption bands in Nujol suspension at 1680(s) and 2240(w), and in chloroform solution at 1690(s) and 2240(w) cm.$^{-1}$; Rabcewicz-Zubkowski and Kaflińska (*Roczn. Chem.*, 1930, **10**, 541) record m. p. 129·5—130°.

A mixture of the keto-nitrile (17·9 g.), *iso*butanol (8·9 g., 20% excess), toluene-*p*-sulphonic acid (1·9 g.), and toluene (250 c.c.) was boiled under reflux for 24 hr., the Dean and Stark apparatus being used, and then worked up in the usual way. On removal of the solvent under reduced pressure the neutral fraction largely crystallized; trituration with light petroleum yielded β-iso*butoxy*-β-p-*chlorophenylacrylonitrile*, which separated from ligroin in colourless plates

(12·9 g., 55%), m. p. 81—83°, absorption bands (Nujol suspension) at 1590 and 2200 cm.$^{-1}$ (Found: C, 66·3; H, 5·8; N, 6·0. $C_{13}H_{14}ONCl$ requires C, 66·2; H, 6·0; N, 5·9%). The combined mother-liquors were fractionated, yielding a further quantity (7·7 g., 33%) of mixed stereoisomers as a colourless oil, b. p. 129—132°/0·4 mm., n_D^{21} 1·5508—1·5558. On redistillation all fractions partly crystallised, and trituration with light petroleum gave more (1·2 g.) of the solid stereoisomer; the liquid stereoisomer was not obtained pure.

α-p-*Chlorobenzoyl*-α-p-*chlorophenylacetonitrile* (4 : 4′-*dichlorocyanodeoxybenzoin*) (IV; R = R′ = *p*-Cl·C_6H_4).—To freshly prepared alcohol-free sodium ethoxide (from 2·53 g. of sodium) was added *p*-chlorophenylacetonitrile (15·2 g.) in dry benzene (100 c.c.), followed by ethyl *p*-chlorobenzoate (20·4 g.) in dry benzene (100 c.c.). The benzene–ethanol azeotrope was slowly distilled off through a short fractionating column, the initial volume being maintained by addition of fresh benzene. When all the ethanol had been removed (3 hr.), the mixture was cooled and shaken with water (200 c.c.). The benzene layer was washed with N-sodium hydroxide (50 c.c.), and the combined aqueous solutions were washed with ether and then acidified; α-p-*chlorobenzoyl*-α-p-*chlorophenylacetonitrile*, which separated as a colourless oil (18·7 g., 65%), rapidly solidified. Recrystallisation from aqueous ethanol gave woolly needles, m. p. 135—136° (Found: C, 62·4; H, 3·2; N, 4·8. $C_{15}H_9ONCl_2$ requires C, 62·1; H, 3·1; N, 4·8%).

α-Benzoylphenylacetonitrile (cyanodeoxybenzoin), m. p. 98—99°, was obtained in an analogous manner in 80% yield.

αβ-*Bis*-p-*chlorophenyl*-β-*methoxyacrylonitrile* (III; R = R′ = *p*-Cl·C_6H_4, R″ = Me).—α-*p*-Chlorobenzoyl-α-*p*-chlorophenylacetonitrile (10 g.) was treated with diazomethane (from 10·7 g. of methylnitrosourea) in ether at 5—10°. The reaction was vigorous and the keto-nitrile rapidly dissolved. After being kept overnight at room temperature the ether and excess of diazomethane were distilled off, and the residue largely solidified. Recrystallisation from ligroin gave αβ-*bis*-p-*chlorophenyl*-β-*methoxyacrylonitrile* as long needles (6·5 g., 62%), m. p. 121—122° (Found: C, 63·6; H, 3·6; N, 4·7. $C_{16}H_{11}ONCl_2$ requires C, 63·2; H, 3·6; N, 4·6%). The stereoisomeric enol ether was not isolated in pure form from the mother-liquors.

An attempt to prepare the analogous *iso*butyl ether by the acid-catalysed azeotropic-distillation method was unsuccessful. When a mixture of the keto-nitrile (11·5 g.), *iso*butanol (3·23 g.), toluene-*p*-sulphonic acid (0·75 g.), and toluene (200 c.c.) was boiled under reflux for 16 hr. only a trace of water (0·05 c.c.) was collected and unchanged keto-nitrile (10·8 g.), m. p. 134—136°, was recovered. Cyanodeoxybenzoin was similarly recovered after a 24-hr. period of reflux.

Ethyl β-*Cyano*-α-*methoxy*-β-*phenylacrylate* (III; R = Ph, R′ = CO_2Et, R″ = Me).—Ethyl β-cyano-β-phenylpyruvate (10·85 g.) (*Org. Synth.*, Coll. Vol. II, p. 287) was treated with diazomethane (from 15·5 g. of methylnitrosourea) in ether (350 c.c.) at 10—15°. Next morning the ether and excess of diazomethane were distilled off and the residue was fractionated, yielding *ethyl* β-*cyano*-α-*methoxy*-β-*phenylacrylate* as a pale yellow oil (10·1 g.), b. p. 128°/0·4 mm., n_D^{21} 1·5509 (Found: C, 67·8; H, 5·5; N, 6·2. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·7; N, 6·1%).

An attempt to prepare the analogous *iso*butyl ether by the acid-catalysed azeotropic distillation method was unsuccessful. A mixture of ethyl β-cyano-β-phenylpyruvate (21·7 g.), *iso*butanol (8·9 g., 20% excess), toluene-*p*-sulphonic acid (1·72 g.), and toluene (150 c.c.) was boiled under reflux for 24 hr., the Dean and Stark separator being used. The neutral fraction, isolated in the usual way, gave on distillation colourless oils, (i) (2·51 g.), b. p. 84—88°/0·7 mm., and (ii) (5·23 g.), b. p. 116—123°/0·6 mm. On redistillation, fraction (i) yielded *iso*butyl phenylacetate, b. p. 65°/0·3 mm., $n_D^{19.5}$ 1·4892 (Found: C, 74·8; H, 8·3. Calc. for $C_{12}H_{16}O_2$: C, 75·0; H, 8·4%), and fraction (ii) gave *iso*butyl toluene-*p*-sulphonate, b. p. 125—127°/1 mm., n_D^{22} 1·5108 (Found: C, 57·6; H, 7·1; S, 14·9. Calc. for $C_{11}H_{16}O_3S$: C, 57·9; H, 7·1; S, 14·0%).

1-iso*Butoxy*-2-*cyano*cyclo*hex*-1-*ene*.—Cyano*cyclo*hexanone was obtained in low yield by bromination of *cyclo*hexanone in the cold and treatment of the crude bromo-ketone with potassium cyanide in aqueous ethanol (cf. Meyer, *Helv. Chim. Acta*, 1933, **16**, 1291). A mixture of cyano*cyclo*hexanone (3·9 g.), *iso*butanol (2·8 g.), toluene-*p*-sulphonic acid (0·6 g.), and toluene (150 c.c.) was boiled under reflux in the manner described above for 17 hr. On distillation, the neutral fraction gave 1-iso*butoxy*-2-*cyano*cyclo*hex*-1-*ene* as a colourless oil (4·74 g., 84%), b. p. 89—90°/0·4 mm., n_D^{18} 1·4908 (Found: C, 73·8; H, 9·8; N, 8·0. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·6; N, 7·8%).

3-*Cyano*-2-*methoxycamph*-2-*ene*.—Cyanocamphor (8·85 g.), prepared by Lapworth's method (*J.*, 1900, **77**, 1058), was treated with excess of diazomethane (from 15·5 g. of methylnitrosourea) in ether (250 c.c.); addition of methanol (40 c.c.) appeared to increase the rate of reaction. After 18 hours at room temperature, the solvent and excess of diazomethane were distilled off

and the residue, dissolved in ether, was washed with N-sodium hydroxide, unchanged cyanocamphor (0·52 g.) being removed. Evaporation of the ethereal solution then gave 3-cyano-2-methoxycamph-2-ene (8·94 g., 94%; m. p. 58°), crystallising from light petroleum in large colourless prisms, m. p. 62—63°, absorption bands (in $CHCl_3$) at 1620 and 2210 cm.$^{-1}$ (Found: C, 75·8; H, 9·0; N, 7·3. Calc. for $C_{12}H_{17}ON$: C, 75·4; H, 9·0; N, 7·3%). Haller and Minguin (*Compt. rend.*, 1894, **118**, 690) record m. p. 63° for this substance isolated from admixture with the *C*-methyl compound, obtained by methylation of cyanocamphor with sodium methoxide–methyl iodide.

An attempt to prepare the analogous *iso*butyl ether by the acid-catalysed azeotropic-distillation method failed. A mixture of cyanocamphor (8·85 g.), *iso*butanol (4·45 g.), toluene-*p*-sulphonic acid (7·75 g.), and benzene (200 c.c.) was refluxed for 24 hr. in the manner already described. The cooled mixture was washed with alkali in the usual way and fractionated, yielding an oil (5·3 g.), b. p. 110—130°/0·4 mm., n_D^{24} 1·4835—1·4682, which contained sulphur (? *iso*butyl toluene-*p*-sulphonate) and from which no pure material could be isolated. Acidification of the alkaline washings and crystallisation of the precipitate from aqueous ethanol gave unchanged cyanocamphor (4·8 g.; m. p. 127—128°).

2 : 4-*Diamino*-6-*methyl*-5-*phenylpyrimidine* (I; R = Ph, R′ = Me).—Guanidine nitrate (6·6 g.) and β-*iso*butoxy-α-phenylcrotononitrile (10·7 g.) were added in succession to a solution of sodium ethoxide (from 1·75 g. of sodium) in absolute ethanol (50 c.c.), and the mixture was boiled under reflux for 18 hr. The solvent was removed under reduced pressure, water (50 c.c.) was added, and pure 2 : 4-diamino-6-methyl-5-phenylpyrimidine (9·3 g., 93%), m. p. 250—252°, was obtained by washing the precipitate on the filter with water and ether until it was colourless (Found: C, 66·0; H, 6·0. Calc. for $C_{11}H_{12}N_4$: C, 66·0; H, 6·0%). Russell and Hitchings (*loc. cit.*) record m. p. 249—251° for this substance prepared from the enol methyl ether.

2 : 4-*Diamino*-5-*chlorophenyl*-6-*ethylpyrimidine* (*Pyrimethamine*) (II).—Guanidine nitrate (1·34 g.) and 3-*iso*butoxy-2-*p*-chlorophenylpent-2-enonitrile (2·64 g.) were added in succession to a solution of sodium ethoxide (from 0·25 g. of sodium) in ethanol (50 c.c.), and the mixture was boiled under reflux for 18 hr. The solvent was removed and the residue was suspended in a mixture of ether (20 c.c.) and water (20 c.c.), the solid (2·24 g., 90%), m. p. 234—236°, being collected and washed with ether and water and dried. Recrystallisation from *iso*butanol yielded 2 : 4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine as colourless flattened needles, m. p. and mixed m. p. 235—236° (Found: C, 57·7; H, 5·1. Calc. for $C_{12}H_{13}N_4Cl$: C, 57·9; H, 5·3%). Russell and Hitchings (*loc. cit.*) record m. p. 233—234°.

2 : 4-*Diamino*-6-p-*chlorophenylpyrimidine* (VI).—Guanidine hydrochloride (4·05 g.) and β-*iso*butoxy-β-*p*-chlorophenylacrylonitrile (10 g.) were added in succession to a solution of sodium ethoxide (from 0·98 g. of sodium) in ethanol (175 c.c.), and the mixture was boiled under reflux for 18 hr. The solvent was removed and the residue was distributed between ether (200 c.c.) and water (100 c.c.). Addition of 10N-hydrochloric acid to the ethereal extract precipitated 2 : 4-*diamino*-6-p-*chlorophenylpyrimidine hydrochloride* (2·9 g.) which separated from water or from methanol–ethyl acetate in colourless needles, m. p. 291—292° (Found: C, 43·4; H, 4·3; N, 20·1; Cl, 26·1. $C_{10}H_9N_4Cl,HCl,H_2O$ requires C, 43·7; H, 4·4; N, 20·4; Cl, 25·8%). The free *base* separated on addition of 2N-sodium hydroxide to a hot aqueous solution of the hydrochloride and crystallised from aqueous ethanol in colourless needles, m. p. 162—163° (Found: C, 54·2; H, 4·2; N, 25·5. $C_{10}H_9N_4Cl$ requires C, 54·4; H, 4·1; N, 25·4%).

2 : 4-*Diamino*-5 : 6-*bis*-p-*chlorophenylpyrimidine* (VII).—Guanidine hydrochloride (1·73 g.) and αβ-bis-*p*-chlorophenyl-β-methoxyacrylonitrile (5·0 g.) were added in succession to a solution of sodium ethoxide (from 0·42 g. of sodium) in absolute ethanol (50 c.c.), and the mixture was boiled under reflux for 3 hr. The solvent was removed under reduced pressure and the residue was shaken with a mixture of ether (100 c.c.) and water (100 c.c.). The 2 : 4-*diamino*-5 : 6-*bis*-p-*chlorophenylpyrimidine* (3·0 g.), which separated, was collected and washed with ether and with water. Recrystallisation from methoxyethanol gave colourless needles, m. p. 290—292°, which powdered on drying at 100° (Found: C, 58·5; H, 3·8; N, 16·9. $C_{16}H_{12}N_4Cl_2$ requires C, 58·0; H, 3·7; N, 16·9%).

Evaporation of the ethereal layer and ethereal washings gave a pale yellow solid (3·3 g.) which separated from ligroin in colourless needles, m. p. 109—110°, and proved to be αβ-*bis*-p-*chlorophenyl*-β-*ethoxyacrylonitrile* (Found: C, 64·2; H, 4·0; N, 4·1; Cl, 22·0. $C_{17}H_{13}ONCl_2$ requires C, 64·2; H, 4·1; N, 4·4; Cl, 22·3%). The m. p. was depressed on admixture with the methyl ether, m. p. 121—122°, to 97—102°.

2 : 4-*Diamino*-5 : 6 : 7 : 8-*tetrahydroquinazoline* (VIII).—(*a*) 1-*iso*Butoxy-2-cyano*cyclo*hex-1-ene was recovered unchanged after being boiled with guanidine in ethanol for 4 hr.

(*b*) Guanidine hydrochloride (3·2 g.) and 1-*iso*butoxy-2-cyano*cyclo*hex-1-ene (5·0 g.) were added in succession to a solution of sodium ethoxide (from 0·77 g. of sodium) in absolute ethanol (75 c.c.), and the mixture was heated in a stainless steel bomb tube at 160—165° (bath) for 2 hr. The cooled contents of the tube were washed out with ethanol and taken to dryness under reduced pressure. The residue was shaken with ether (25 c.c.) and water (25 c.c.), and the solid (0·30 g.) was collected. Recrystallisation from aqueous ethanol yielded pure 2 : 4-*diamino*-5 : 6 : 7 : 8-*tetrahydroquinazoline* as colourless needles, m. p. 241—243°, which became opaque on drying at 100° (Found : C, 58·2; H, 7·5. $C_8H_{12}N_4$ requires C, 58·5; H, 7·4%). Fractionation of the ethereal solution gave (apparently) unchanged enol ether (4·5 g.), n_D^{23} 1·4790.

2 : 6-*Diaminocamph*-2′-*eno*(2′ : 3′-4 : 5)*pyrimidine* (IX).—(*a*) 3-Cyano-2-methoxycamph-2-ene was recovered quantitatively after being boiled with guanidine in ethanol for 4 hr.

(*b*) Guanidine hydrochloride (2·33 g.) and 3-cyano-2-methoxycamph-2-ene (4·2 g.) were added successively to a solution of sodium ethoxide (from 0·56 g. of sodium) in absolute ethanol (75 c.c.), and the mixture was heated in the steel bomb at 160—170° (bath) for 3 hr. The mixture was worked up as before and the residue was partitioned between ether and water. Extraction of the ethereal solution with N-hydrochloric acid, basification, and extraction with ether gave 2 : 6-diaminocamph-2′-eno(2′ : 3′-4 : 5)pyrimidine as a colourless crystalline solid (0·19 g.), which separated from aqueous ethanol in colourless laths, m. p. 241—242° (Found : C, 66·1; H, 8·3. Calc. for $C_{12}H_{18}N_4$: C, 66·0; H, 8·3%). Mayer (*Ann. Sci. Univ. Jassy*, 1937, Pt. I, **23**, 279; *Chem. Zentr.*, 1937, II, 1575) records m. p. 244° for this substance prepared in very low yield from camphorcarboxylic acid.

The authors are indebted to Mr. R. J. Clark for preparative assistance, and to Miss A. E. Wilson for carrying out infra-red spectrometric determinations.

National Institute for Medical Research,
The Ridgeway, Mill Hill, London, N.W.7. [*Received, June 27th*, 1953.]

---

708. *Melanin and Its Precursors. Part VII.* Synthesis of Methylated 5 : 6-Dihydroxyindoles, β-(4 : 5-Dihydroxy-2-methylphenyl)alanine, and Related Amines.*

By R. I. T. Cromartie and John Harley-Mason.

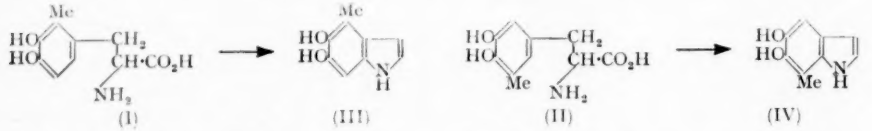
5 : 6-Dihydroxy-4- and -7-methylindole have been obtained by oxidation of 3 : 4-dihydroxy-2- and -5-methylphenylalanine. 5 : 6-Dihydroxy-4 : 7-dimethylindole has been prepared by a seven-stage synthesis from *p*-xyloquinone. β-(4 : 5-Dihydroxy-2-methylphenyl)alanine, 2-(4 : 5-dihydroxy-2-methylphenyl)ethylamine and its *N*-benzyl derivative have been prepared by conventional methods from 4 : 5-dimethoxy-2-methylbenzaldehyde.

In order to obtain information on the structure of tyrosine-melanin which is formed by the oxidative polymerisation of 5 : 6-dihydroxyindole, a comparative study of the oxidation of a series of 5 : 6-dihydroxyindoles substituted by methyl groups in each of the five available positions was envisaged. 5 : 6-Dihydroxy-1-, -2- and -3-methylindole have previously been prepared (Harley-Mason, *J.*, 1950, 1276; Beer, McGrath, Robertson, and Woodier, *J.*, 1949, 2061), and the syntheses of 5 : 6-dihydroxy-4- and -7-methyl- and -4 : 7-dimethyl-indole, now reported, complete the series.

Conversion of β-(3 : 4-dihydroxyphenyl)alanine into 5 : 6-dihydroxyindole was described by Bu'Lock and Harley-Mason (Part III; *J.*, 1951, 2248), though the yield was poor and erratic. With improved technique this reaction has now been applied to 3 : 4-dihydroxy-2- and -5-methylphenylalanine (I and II) (preparation, Cromartie and Harley-Mason Part IV, *J.*, 1952, 1052), giving 5 : 6-dihydroxy-4- and -7-methylindole (III and IV)

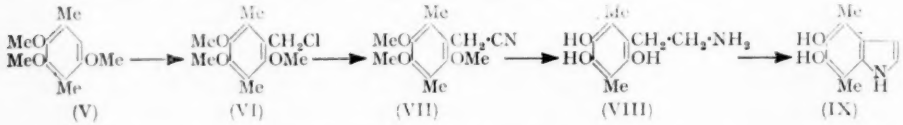
* Part VI, *J.*, 1953, 200.

respectively. For the preparation of 5 : 6-dihydroxy-4 : 7-dimethylindole the new dihydroxyindole synthesis described by Harley-Mason (Part VI *) was employed. Thiele acetylation of 2 : 5-dimethyl-*p*-benzoquinone gave triacetoxy-*p*-xylene which on treatment with a large excess of methyl sulphate and alkali gave trimethoxy-*p*-xylene (V). Chloromethylation then gave 2 : 4 : 5-trimethoxy-3 : 6-dimethylbenzyl chloride (VI), converted by



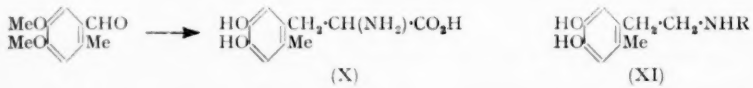
(I) (III) (II) (IV)

potassium cyanide into the corresponding cyanide (VII). Hydrogenation of (VII) gave 2-(2 : 4 : 5-trimethoxy-3 : 6-dimethylphenyl)ethylamine, demethylated by hydrobromic acid to the corresponding trihydroxy-amine (VIII). On oxidation with potassium ferricyanide this gave 5 : 6-dihydroxy-4 : 7-dimethylindole (IX) in good yield.



(V) (VI) (VII) (VIII) (IX)

The remaining monomethylated 3 : 4-dihydroxyphenylalanine, *i.e.*, β-(4 : 5-dihydroxy-2-methylphenyl)alanine (X) has now been prepared by a method similar to that employed for the other two, starting from 4 : 5-dimethoxy-2-methylbenzaldehyde. The corresponding amine, 2-(4 : 5-dihydroxy-2-methylphenyl)ethylamine (XI; R = H) and its *N*-benzyl derivative (XI; R = benzyl) have also been synthesised *via* 4 : 5-dimethoxy-2-methyl-β-



(X) (XI)

nitrostyrene. On oxidation with potassium ferricyanide or silver oxide none of the last three compounds gave any indole derivative : the methyl group of course prevents cyclisation to a 5 : 6-dihydroxyindole and it is particularly significant that the alternative cyclisation to give a 6 : 7-dihydroxyindole does not occur. This indicates that the product obtained by oxidation of (II) is in fact (IV) and not a 6 : 7-dihydroxyindole. Evidently the methyl group does not provide sufficient steric hindrance to prevent condensation at the position *ortho* to it, though it should be noted that the yield in this case is low.

Experimental

5 : 6-*Dihydroxy*-4-*methylindole* (III).—To a solution of β-(3 : 4-dihydroxy-2-methylphenyl)-alanine monohydrate (Cromartie and Harley-Mason, *J.*, 1952, 1052) (0·46 g., 0·002 mole) and sodium hydrogen carbonate (0·17 g., 0·002 mole) in water (8 c.c.), potassium ferricyanide (2·56 g., 0·008 mole), and sodium hydrogen carbonate (0·7 g., 0·008 mole) in water (30 c.c.) were added. A brisk evolution of carbon dioxide occurred and the solution became deep red. After 20 min. a solution of zinc sulphate (6 g.) in water (16 c.c.) was added and the mixture shaken until the red colour had faded to a greyish-brown (about 15 min.). After addition of a little sodium dithionite to prevent oxidation, the zinc ferrocyanide was filtered off and washed well with water. The combined filtrate and washings were extracted with ethyl acetate (3 × 30 c.c.), the extract was dried over alkali-free sodium sulphate, and the solvent removed under hydrogen. The residue was sublimed at 0·001 mm., most of the product coming over at 180—190°, though a further small fraction was obtained at 250°. Resublimation afforded 5 : 6-*dihydroxy*-4-*methylindole* (0·13 g., 40%) as colourless needles, m. p. 146—149° (decomp.) (Found : C, 66·6; H, 5·7; N, 8·7. $C_9H_9O_2N$ requires C, 66·3; H, 5·5; N, 8·6%). The material gave a violet Ehrlich reaction and slowly decomposed.

5 : 6-*Dihydroxy*-7-*methylindole* (IV).—β-(3 : 4-Dihydroxy-5-methylphenyl)alanine monohydrate (0·46 g.) (Cromartie and Harley-Mason, Part IV, *loc. cit.*) was oxidised as described above, giving a deep violet solution, which was treated with zinc sulphate and worked up as above. **5 : 6-*Dihydroxy*-7-*methylindole*** (0·04 g., 12%) formed colourless needles, m. p. 108—109°, giving a violet Ehrlich reaction (Found : C, 66·1; H, 5·3; N, 8·7%). The material was less stable than the 4-methyl isomer and rapidly decomposed to a black mass.

2 : 4 : 5-*Trimethoxy*-3 : 6-*dimethylbenzyl Cyanide*.—Triacetoxy-*p*-xylene (Erdtman, *Proc. Roy. Soc.*, 1934, *A*, **143**, 177) (27 g., 0·1 mole) and 20% aqueous sodium hydroxide solution (200 c.c.) were boiled for 30 min. under nitrogen. Into the solution thus obtained were run alternately methyl sulphate (140 c.c., 1·5 mole) and 20% aqueous sodium hydroxide (300 c.c.) in small portions during 5 hr. After a further 2 hours' boiling the mixture was diluted with water and extracted with ether (2 × 500 c.c.). The extract was dried (Na_2SO_4) and the solvent removed, leaving an oil which was distilled under reduced pressure. ***Trimethoxy*-p-*xylene*** (10·5 g., 56%) formed an almost colourless oil, b. p. 135°/22 mm. (Found : C, 67·5; H, 8·5. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·1%).

Trimethoxy-*p*-xylene (7 g.), 40% formaldehyde solution (30 c.c.), and concentrated hydrochloric acid (50 c.c.) were mixed and saturated with hydrogen chloride at 0°. The homogeneous solution thus obtained was heated at 50—60° for 4 hr. and then kept overnight at 0°. The oil which separated solidified to a waxy mass of 2 : 4 : 5-trimethoxy-3 : 6-dimethylbenzyl chloride (8 g., 93%) which was collected and washed. The chloride (7·5 g.) was boiled for 3 hr. under reflux with potassium cyanide (22 g.) in water (40 c.c.) and ethanol (150 c.c.). The mixture was then poured on crushed ice, and the brownish solid collected and twice recrystallised (charcoal) from light petroleum (b. p. 40—60°), giving **2 : 4 : 5-*trimethoxy*-3 : 6-*dimethylbenzyl cyanide*** (3·7 g., 52%), colourless prisms, m. p. 62° (Found : C, 66·1; H, 7·5; N, 6·0. $C_{13}H_{17}O_3N$ requires C, 66·3; H, 7·5; N, 6·0%).

5 : 6-*Dihydroxy*-4 : 7-*dimethylindole* (IX).—The foregoing cyanide (3·2 g.), dissolved in dry ethanol (70 c.c.) saturated with ammonia, was hydrogenated over Raney nickel at 75°/100 atm. for 10 hr. The filtered solution was evaporated to dryness, the residue dissolved in dry ethanol, and hydrogen chloride passed in, precipitating **2-(2 : 4 : 5-*trimethoxy*-3 : 6-*dimethylphenyl*)-*ethylamine hydrochloride*** (2·5 g.), which after recrystallisation from ethanol–ether formed needles m. p. 266—267° (decomp.) (Found : C, 57·1; H, 8·4; N, 5·0. $C_{13}H_{22}O_3NCl$ requires C, 56·6; H, 8·0; N, 5·1%).

The hydrochloride (1·5 g.) was refluxed for 1 hr. with hydrobromic acid (*d* 1·49; 10 c.c.). After being kept overnight at 0°, the dark solid was collected and twice recrystallised (charcoal) from ethanol–ether, giving **2-(2 : 4 : 5-*trihydroxy*-3 : 6-*dimethylphenyl*)*ethylamine hydrobromide*** (1·1 g.) as small prisms, m. p. 227—228° (decomp.) (Found : C, 42·8; H, 5·6. $C_{10}H_{16}O_3NBr$ requires C, 43·2; H, 5·8%). To a solution of the hydrobromide (10·37 g.) in water (25 c.c.), a solution of potassium ferricyanide (0·8 g.) and sodium hydrogen carbonate (0·34 g.) in water (20 c.c.) was added. The intensely violet solution which resulted was kept for 24 hr. under hydrogen, the colour fadlng considerably. After addition of a little sodium dithionite, the solution was extracted with ethyl acetate (2 × 40 c.c.), the extract dried (Na_2SO_4), and the solvent removed.

The greyish solid residue was sublimed at 150°/0·01 mm. Resublimation of the product at 130°/0·001 mm. gave **5 : 6-*dihydroxy*-4 : 7-*dimethylindole*** (0·14 g., 60%) as colourless needles, m. p. 170° (preheated bath; decomp.) (Found : C, 68·5; H, 6·6; N, 8·0. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·3; N, 7·9%). The solid was more stable than either of the monomethylated compounds; with Ehrlich's reagent a deep blue colour was given.

β-(4 : 5-*Dihydroxy*-2-*methylphenyl*)*alanine* (X).—4-(4 : 5-Dimethoxy-2-methylbenzylidene)-2-phenyloxazolone (Sugasawa and Shigehara, *Ber.*, 1941, **74**, 459) (12·5 g.) in ethanol (90 c.c.) was heated on a water-bath with 5% aqueous sodium hydroxide (90 c.c.). After cooling, the pale yellow solution was treated slowly with 20% hydrochloric acid until no more solid was precipitated. ***α*-Benzamido-4 : 5-*dimethoxy*-2-*methylcinnamic acid*** was collected and recrystallised from aqueous ethanol, giving cream-coloured needles (11·5, 87%), m. p. 212—214° (decomp.) (Found : C, 66·7; H, 5·8. $C_{19}H_{19}O_5N$ requires C, 66·9; H, 5·6%).

A solution of the foregoing acid (4·5 g.) in N-sodium hydroxide (160 c.c.) was diluted to 600 c.c. and hydrogenated over Raney nickel at room temperature and 80 atm. After filtration, the solution was acidified and kept overnight at 0°. The precipitate was collected and recrystallised from ethanol, giving ***α*-benzamido-β-(4 : 5-*dimethoxy*-2-*methylphenyl*)*propionic acid*** (3·8 g., 85%) as fine colourless needles, m. p. 203° (preheated bath) with decomposition to a bright yellow melt (Found : C, 66·2; H, 6·3. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·1%).

The foregoing acid (0·75 g.) was refluxed for 75 min. with hydrobromic acid (*d* 1·49; 10 c.c.). The cooled solution was diluted with water and extracted with ether to remove benzoic acid. The aqueous layer was evaporated to dryness under hydrogen, the residue dissolved in water, and the evaporation repeated to remove the last traces of hydrobromic acid. The pale buff crystalline residue was dissolved in water (8 c.c.) and brought to pH 5 by dropwise addition of pyridine. Evaporation at room temperature gave a syrup to which ethanol (10 c.c.) was added. Insoluble impurities were removed by filtration and the filtrate slowly deposited the amino-acid. Recrystallised from water containing sulphur dioxide, **4 : 5-*dihydroxy-2-methylphenyl-alanine*** (0·23 g., 46%) formed colourless prisms, probably a hydrate, dehydrated at 100° in a vacuum to the anhydrous acid, m. p. 269° with effervescence (Found : C, 56·5; H, 6·0; N, 6·8. $C_{10}H_{13}O_4N$ requires C, 56·8; H, 6·2; N, 6·6%).

4 : 5-*Dihydroxy-2-methylphenylethylamine.*—A solution of 4 : 5-dimethoxy-2-methylbenzaldehyde (Gattermann, *Annalen*, 1907, **357**, 370) (12 g.), nitromethane (6 g.), and ammonium acetate (3 g.) in acetic acid (70 c.c.) was refluxed for 2 hr. and then poured into water. The precipitated product was collected and recrystallised from ethanol, giving **4 : 5-*dimethoxy-2-methyl-β-nitrostyrene*** (8 g.) as deep golden-yellow needles, m. p. 155° (Found : C, 59·3; H, 5·9. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·8%). The nitrostyrene (8 g.) was placed in a Soxhlet thimble and extracted under reflux into a solution of lithium aluminium hydride (5·5 g.) in ether (400 c.c.) during 10 hr. The mixture was decomposed with sodium potassium tartrate solution, the ethereal layer separated and dried (KOH), and the solvent removed, leaving 4 : 5-dimethoxy-2-methylphenylethylamine (5·8 g., 83%) as a wax. A portion was converted into the *hydrochloride*, which formed prisms, m. p. 181—182·5°, from ethanol–ether (Found: C, 57·2; H, 7·9. $C_{11}H_{18}O_2NCl$ requires C, 57·0; H, 7·8%). The amine (1 g.) was refluxed with hydrobromic acid (*d* 1·49; 10 c.c.) for 1 hr., and the resulting solution kept overnight at 0°. The dark solid which had separated was collected and twice recrystallised (charcoal) from ethanol–ether, giving **β-(4 : 5-*dihydroxy-2-methylphenyl)ethylamine hydrobromide*** (0·75 g.) as pale brown needles m. p. 213—216° (decomp.) (Found : C, 43·5; H, 5·6. $C_9H_{14}O_2NBr$ requires C, 43·5; H, 5·6%).

N*-Benzyl-β-(4 : 5-*dihydroxy-2-methylphenyl)ethylamine.—A mixture of the above dimethoxyamine (1·5 g.) and freshly distilled benzaldehyde (0·9 c.c.) was heated on the steam-bath for 45 min. and then kept overnight in a vacuum-desiccator. The resulting solid Schiff's base in ethanol (30 c.c.) was hydrogenated over Raney nickel at room temperature and 80 atm. for 5 hr. The filtered solution was concentrated and hydrogen chloride passed in. Addition of ether precipitated *N*-benzyl-β-(4 : 5-dimethoxy-2-methylphenyl)ethylamine hydrochloride. The crude hydrochloride (1 g.) was demethylated as in the preceding case. ***N*-Benzyl-β-(4 : 5-*dihydroxy-2-methylphenyl)ethylamine hydrobromide*** formed prisms, m. p. 152—153° (Found : C, 56·5; H, 5·9. $C_{16}H_{20}O_2NBr$ requires C, 56·8; H, 5·9%).

Oxidation Experiments.—4 : 5-Dihydroxy-2-methylphenylalanine was oxidised with potassium ferricyanide under the conditions described above for the other dihydroxyphenylalanines. An orange-red solution was obtained, which was, however, not decolorised on the addition of zinc sulphate. The ethyl acetate extract gave only a trace of solid on evaporation and gave a negative Ehrlich reaction. The dihydroxy-amines above behaved similarly and no trace of an indole derivative could be detected.

One of us (R. I. T. C.) thanks the Department of Scientific and Industrial Research for a Maintenance grant.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, July 10th*, 1953.]

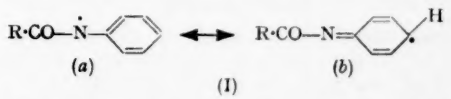
709. *Properties and Reactions of Free Alkyl Radicals in Solution. Part VI.* Reactions with N-Halogenoanilides.*

By M. C. Ford, L. J. Hunt, and William A. Waters.

2-Methoxycarbonyl-2-propyl radicals abstract the *N*-halogen atom from an *N*-halogeno-anilide, giving the corresponding methyl α-halogeno*iso*butyrate together with products derived from the newly formed acylamino-radical, •NAr•COR. From *N*-chloroacetanilide there is obtained methyl α-*p*-acetamidophenyl*iso*butyrate. *N*-Chlorobenzanilide gives 4-benzamido-*N*-benzoyldiphenylamine, and a similar product results from *N* : 2′ : 4′-trichlorobenzanilide. *N* : 2′ : 4′ : 6′-Tetrachlorobenzanilide yields both benzoyl chloride and 3 : 5-dichloro-1 : 4-benzoquinone 1-(2 : 4 : 6-trichloroanil). These results indicate that acylamino-radicals are mesomeric, and couple to give C–C or N–C, and not N–N, bonds.

The study of the reactions of free alkyl radicals with " positive " halogen compounds (Part III, *J.*, 1952, 2240) has now been extended to an investigation of the decomposition of dimethyl αα′-azo*iso*butyrate in the presence of a number of *N*-halogenoanilides. It has been found that 2-methoxycarbonyl-2-propyl radicals $MeO_2C{\cdot}CMe_2{\cdot}$ abstract the nitrogen-linked halogen atom, forming the corresponding methyl α-halogeno*iso*butyrate in 35—50% yield, together with products of different types derived from the newly-formed nitrogen radicals (I). Sufficient azo-ester to ensure complete reaction of the *N*-halogenoanilide was always used.

The nitrogenous reaction products were never the hydrazine derivatives which would have resulted from nitrogen–nitrogen union of the acylamino-radicals (I) of canonical form



(I)

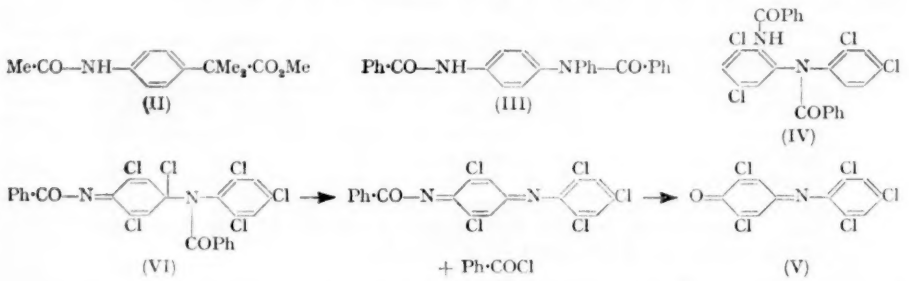
(*a*) but were invariably products containing stable carbon–nitrogen or carbon–carbon bonds indicative of reaction through forms such as (*b*). Thus *N*-chloroacetanilide yielded 6% of methyl α-*p*-acetamidophenyl*iso*butyrate (II) by reaction of a 2-methoxycarbonyl-2-propyl radical with a radical in form (I*b*), whereas *N*-chlorobenzanilide under similar conditions gave 26% of 4-benzamido-*N*-benzoyldiphenylamine (III) by interaction of two acylamino-radicals in forms (*a*) and (*b*) respectively. From the analogous reaction with *N*-bromoacetanilide, however, only methyl α-bromo*iso*butyrate and *p*-bromoacetanilide could be isolated.

N : 2′ : 4′-Trichlorobenzanilide gave 54% of a product similar to (III), undoubtedly 2-benzamido-*N*-benzoyl-3 : 5 : 2′ : 4′-tetrachlorodiphenylamine (IV), whilst *N* : 2′ : 4′ : 6′-tetrachlorobenzanilide yielded 4% of 3 : 5-dichloro-1 : 4-benzoquinone 1-(2 : 4 : 6-trichloroanil) (V) and 35% of benzoyl chloride. These last products clearly result from the expected intermediate (VI); hydrolysis of the Ph·CO·N: group may well have occurred during the chromatographic separation of the reaction products. Intractable substances of higher molecular weight were also formed, and unfortunately these sometimes constituted the major part of the reaction product. As noted previously (Bickel and Waters, *Rec. Trav. chim.*, 1950, **69**, 312), poly(methyl methylacrylate) is to be expected as an end product in the decomposition of the azo-ester.

The structure of (II) has been established by hydrolysis to α-*p*-aminophenyl*iso*butyric acid which (i) gave only a *di*bromo-derivative and (ii) by hypophosphite deamination yielded α-phenyl*iso*butyric acid, identical with an authentic specimen. α-*o*-Aminophenyl-*iso*butyric acid would, by ring closure to 3 : 3-dimethyloxindole, have exhibited quite different properties. The dibenzoyl derivative (IV) lost only one benzoyl group on hydrolysis; the product gave a typical " diphenylamine-blue " colour reaction, and it can

* Part V, *J.*, 1952, 4666.

therefore be concluded that the hydrolysis had removed the benzoyl group attached to the secondary nitrogen of the diphenylamine system. The structure of (III) has been fully established by direct comparison with a synthetic product obtained from *N*-benzoyl-4-nitro-



diphenylamine (Lellmann, *Ber.*, 1882, **15**, 826) by reduction and further benzoylation. The amides (III) and (IV) give similar infra-red spectra, from which the presence of N–H links and two differently arranged C=O links (in –NH·CO– and =N·CO–) was evident. The anil (V), m. p. 142·5°, was prepared synthetically by condensation of 2 : 6-dichloro-1 : 4-benzoquinone with *s*-trichloroaniline. The isomeric 2 : 6-dichloro-1 : 4-benzoquinone 1-(2 : 4 : 6-trichloroanil), which could also result by this condensation, but is not formed, presumably owing to the steric effect of the flanking chlorine atoms in the quinone, is described by Bradfield, Cooper, and Orton (*J.*, 1927, 2854) as " bronzy-red needles, m. p. 163°."

Experimental

Interaction of N-Chloroacetanilide and Dimethyl αα′-Azoisobutyrate.—A solution of the *N*-chloroanilide (purity 100%; 17·0 g., 0·1 mole) and the azo-ester (34·5 g., 0·15 mole) in dry benzene (" AnalaR "; 50 ml.) was gradually heated during 0·5 hr. in such a way as to produce a regular evolution of nitrogen, and finally refluxed for 1·5 hr. The crystalline precipitate obtained on storage of the product overnight at 0° was combined with the small quantities of solid obtained by successive treatments of the mother-liquor with light petroleum (b. p. 80—100°). The whole when recrystallised twice from benzene containing a little light petroleum gave *methyl* α-p-*acetamidophenylisobutyrate* (II) (1·4 g., 6%), glistening plates, m. p. 164° (Found: C, 66·6; H, 7·0; N, 5·8. $C_{13}H_{17}O_3N$ requires C, 66·4; H, 7·2; N, 5·95%). Removal of the solvents from the combined residues gave an oil which afforded methyl α-chloro*iso*but rate (4·8 g., 35% calc. on the chloroamide), b. p. 38°/17 mm., characterised by conversion into α-chloro*iso*butyramide, m. p. 119—121° (Found: Cl, 29·2. Calc. for C_4H_8ONCl: Cl, 29·2%). After removal of dimethyl tetramethylsuccinate (5·7 g.) a distillate, b. p. 110—125°/0·25—0·2 mm., was obtained which on trituration with light petroleum gave acetanilide (0·45 g.), m. p. and mixed m. p. 114°; a viscous residue (12·7 g.) remained.

Hydrolysis of Methyl α-p-*Acetamidophenylisobutyrate.*—(a) *Alkaline hydrolysis.* The acetamido-ester (0·9 g.) in alcohol (20 ml.) was treated with potassium hydroxide (1·5 g.) in water (7·5 ml.) and refluxed for 2 hr. Evaporation of the product to dryness under diminished pressure and acidification of the residue gave α-p-*acetamidophenylisobutyric acid*, which after crystallisation from water and then from toluene formed colourless blades, m. p. 168—169° (Found: C, 65·6; H, 7·0; N, 6·2. $C_{12}H_{15}O_3N$ requires C, 65·1; H, 6·8; N, 6·3%).

(b) *Acid hydrolysis.* The acetamido-ester (1·35 g.) was refluxed for 3 hr. with hydrochloric acid (36%; 25 ml.). The solution was evaporated to dryness under reduced pressure and the residue was dissolved in aqueous ammonia and decolorised (charcoal). Acidification gave α-p-*aminophenylisobutyric acid*, which on crystallisation from water and then from toluene gave buff needles (0·8 g.), m. p. 168—169° (decomp.) (Found: C, 67·4; H, 7·5; N, 7·6. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3; N, 7·8%). Treatment of the amino-acid with acetic anhydride at 100° for 5 min. gave the acetamido-acid, m. p. 168—169°, undepressed in admixture with the sample obtained as above. Benzoylation of the amino-acid under Schotten-Baumann conditions with a slight excess of benzoyl chloride, followed by acidification and refluxing of the solid reaction product with carbon tetrachloride to remove benzoic acid, gave α-p-*benzamido-*

phenylisobutyric acid, which crystallised from aqueous alcohol in plates, m. p. 221·5—223° (Found: C, 71·9; H, 6·19; N, 5·14. $C_{17}H_{17}O_3N$ requires C, 72·1; H, 6·04; N, 4·94%).

Deamination of α-p-*Aminophenylisobutyric Acid.*—To a paste of the amino-acid (0·36 g.) in hydrochloric acid (36%; 4 ml.) and water (4·5 ml.) at 0° was added sodium nitrite (0·15 g.) in water (5 ml.), and the resulting diazo-solution was treated with sodium hypophosphite (3·2 g.) in water (6 ml.). After the addition was complete, nitrogen began to be evolved. The product (0·3 g.), which had crystallised after storage of the mixture overnight at 0°, was washed with water and than had m. p. 74—77°. Crystallisation from water (charcoal) and finally from light petroleum (b. p. 40—60°) gave α-phenyl*iso*butyric acid, m. p. 76·5—78°, undepressed in admixture with an authentic specimen (Brander, *Rec. Trav. chim.*, 1918, **37**, 67) (Found: C, 73·1; H, 7·4. Calc. for $C_{10}H_{12}O_2$: C, 73·1; H, 7·4%).

α-(4-*Amino*-3 : 5-*dibromophenyl*)*isobutyric Acid.*—The amino-acid (0·36 g.) in glacial acetic acid (7 ml.) was gradually treated with a 10% solution of bromine in glacial acetic acid (7 ml.) at room temperature; after 20 min. an excess of bromine was still present. The product was poured into water; the resulting solid crystallised from aqueous alcohol in feathery prisms, m. p. 166·5—168° (Found: Br, 47·1. $C_{10}H_{11}O_2NBr_2$ requires Br, 47·4%).

Interaction of N-*Bromoacetanilide and Dimethyl* αα′-*Azoisobutyrate.*—The decomposition of the azo-ester (10·0 g.) with *N*-bromoacetanilide (purity, 93%; 5·35 g.) in benzene (20 ml.) was carried out as described for the *N*-chloroanilide, and gave rise to methyl α-bromo*iso*butyrate (2·0 g., 48% calc. on the bromoanilide), b. p. 40—47°/11—16 mm., characterised by conversion into α-bromo*iso*butyramide, m. p. 144°, which did not depress the m. p. of an authentic specimen (cf. Part III, *loc. cit.*). The only product which could be isolated from the tarry involatile residue was *p*-bromoacetanilide, m. p. and mixed m. p. 166—168°.

Interaction of N-*Chlorobenzanilide and Dimethyl* αα′-*Azoisobutyrate.*—A solution of the *N*-chloroanilide (purity 97%; 23·2 g., 0·1 mole) and the azo-ester (34·5 g., 0·15 mole) in dry benzene (50 ml.) was gently heated in such a way that the evolution of nitrogen was steady and controlled. After 2·75 hr. only a trace of the chloroanilide remained. Distillation of the resulting orange-yellow solution through a short column gave (i) benzene containing methyl *iso*butyrate (1·4 g.), identified by the method of Bickel and Waters (*loc. cit.*) by preparation of *S*-benzylthiuronium *iso*butyrate, m. p. and mixed m. p. 142—144°, and of *iso*butyranilide, m. p. 104°. The residual oil was repeatedly shaken with light petroleum (b. p. 40—60°), and the combined extracts were fractionated, yielding (ii) methyl α-chloro*iso*butyrate (6·2 g., 45%), b. p. 30—40°/11 mm. (amide, m. p. and mixed m. p. 119—119·5°), (iii) dimethyl tetramethylsuccinate (6·6 g.), b. p. 92—98°/11 mm., m. p. 31—32°, characterised by conversion into di-*S*-benzylthiuronium tetramethylsuccinate, m. p. and mixed m. p. 144—146°, and also into di-*p*-nitrobenzyl tetramethylsuccinate, m. p. and mixed m. p. 146—148°, and (iv) (2·9 g.), b. p. 150—160°/11 mm., consisting largely of trimethyl 2 : 3 : 5-trimethylhexane-2 : 3 : 5-tricarboxylate.

The residue from the light petroleum extraction crystallised from alcohol as colourless prisms (7·1 g.), m. p. 195—200°. This product (2·0 g.) was dissolved in benzene and submitted to chromatographic separation on alumina; elution with benzene afforded a *compound* (0·11 g.), m. p. 176—178° (Found: C, 72·7; H, 4·5; N, 6·6; Cl, 8·3. $C_{26}H_{19}O_2N_2Cl$ requires C, 73·1; H, 4·45; N, 6·6; Cl, 8·3%), and further elution with benzene–chloroform (330 ml., 1 : 1) gave 4-benzamido-*N*-benzoyldiphenylamine (III) (1·46 g., 26% calc. on the chloroanilide), m. p. 202·5—203° (Found, on material dried at 100° *in vacuo*: C, 79·2; H, 5·2; N, 7·2. Calc. for $C_{26}H_{20}O_2N_2$: C, 79·6; H, 5·1; N, 7·1%). The infra-red spectrum, which was identical throughout the range 3·0—15·0 μ with that of the synthetic specimen described below, exhibited the following features: 3·02 μ (N–H); 6·02 and 6·12 μ (amide I bands); 6·25, 6·30, 6·71 μ (aromatic system); 6·55, 6·64 μ (amide II bands). A solution of the material in concentrated sulphuric acid was warmed gently and then cooled; addition of a trace of sodium nitrite then produced an intense "diphenylamine-blue" colour. No colour was produced unless the solution had been previously heated (conversion of :N·COPh into :NH). Hydrolysis of the dibenzoyl compound with 20% alcoholic sulphuric acid for 6 hr. gave a solution from which ethyl benzoate could be distilled in steam; this was characterised by hydrolysis to benzoic acid, m. p. and mixed m. p. 121°; attempts to isolate pure crystalline material from the dark residue were unsuccessful.

Distillation of the ultimate residues from the crystallisation of (III) yielded benzanilide (0·2 g.), b. p. <180°/0·5 mm., which when crystallised from light petroleum had m. p. and mixed m. p. 156—158°. The involatile residue (12 g.) consisted largely of poly(methyl methylacrylate).

Preparation of 4-*Benzamido*-N-*benzoyldiphenylamine* [cf. Bayer & Co., D.R.-P. 296,964 (*Chem. Zentr.*, 1917, **21** (I), 717)].—Granulated tin (40 g.) was added in portions to a mechanically stirred solution of *N*-benzoyl-4-nitrodiphenylamine (Lellmann, *loc. cit.*) (4 g.) in glacial acetic

acid (160 ml.) and hydrochloric acid (36%; 45 ml.) at 90°. When the reaction had subsided, a further quantity (25 ml.) of hydrochloric acid was added and the mixture was heated at 100° for 1 hr. The solution was filtered and made alkaline, and the sold product was isolated and crystallised from aqueous alcohol, giving 4-amino-*N*-benzoyldiphenylamine (66%), m. p. 183·5—184° (Found: C, 78·9; H, 5·7; N, 9·6. Calc. for $C_{19}H_{16}ON_2$: C, 79·2; H, 5·6; N, 9·7%). Bayer & Co. record m. p. 178°. The amino-amide was benzoylated in acetone solution under Schotten–Baumann conditions, yielding 4-benzamido-*N*-benzoyldiphenylamine, m. p. 202—203·5° (Found: C, 79·9; H, 5·2; N, 7·2%). The mixed m. p. with the sample obtained as above was 203°. Biehringer and Busch (*Ber.*, 1902, **35**, 1971) record m. p. 203° for this product, which they obtained by dibenzoylation of 4-aminodiphenylamine.

Interaction of N : 2′ : 4′-*Trichlorobenzanilide and Dimethyl* αα′-*Azoisobutyrate.*—A solution of the *N*-chloroanilide (purity 97%; 18·1 g.) and the azo-ester (15·0 g.) in dry benzene (40 ml.) was gradually heated during 25 min. and finally refluxed for 2 hr.; no chloroanilide remained (negative starch–KI test). On cooling of the pale red solution to 0° and scratching, 2-*benzamido*-N-*benzoyl*-3 : 5 : 2′ : 4′-*tetrachlorodiphenylamine* (IV) (5·55 g.) crystallised; a further quantity (2·85 g.) was obtained by treatment of the mother-liquor with light petroleum. Crystallisation from xylene and then from *iso*amyl alcohol gave colourless prisms (54%), m. p. 220° (Found: C, 59·3, 59·4; H, 3·4, 3·2; N, 5·3; Cl, 26·5. $C_{26}H_{16}O_2N_2Cl_4$ requires C, 58·9; H, 3·0; N, 5·3; Cl, 26·7%). The infra-red spectrum exhibited the following diagnostic features: 3·10 μ (N–H); 5·96 and 6·04 μ (amide I); 6·24, 6·33, 6·40, 6·70 μ (aromatic system); 6·58—6·62 μ (amide II). Distillation of the light petroleum extract gave methyl α-chloro*iso*butyrate (3·2 g., 40%), b. p. 40—43°/18—21 mm. (amide, m. p. and mixed m. p. 119—121°), and dimethyl tetramethylsuccinate (2·4 g.), b. p. 102—112°/15 mm. Chromatography of the ultimate residues gave 2′ : 4′- dichlorobenzanilide (1·1 g.), m. p. and mixed m. p. 117—118°.

Product (IV) (1·0 g.) was refluxed with potassium hydroxide (1·0 g.) in alcohol (40 ml.) for 1·5 hr. Potassium benzoate was slowly precipitated, and on acidification gave benzoic acid, m. p. and mixed m. p. 121°. The filtrate was evaporated and the residue washed with water and repeatedly crystallised from alcohol, giving 2-*benzamido*-3 : 5 : 2′ : 4′-*tetrachlorodiphenylamine* (0·75 g.), colourless plates, m. p. 227·5° (Found: C, 53·6; H, 3·0; N, 6·8; Cl, 33·2. $C_{19}H_{12}ON_2Cl_4$ requires C, 53·6; H, 2·8; N, 6·6; Cl, 33·3%). The addition of a trace of sodium nitrite to a solution of this compound in cold concentrated sulphuric acid gave an intense "diphenylamine-blue" colour.

Interaction of N : 2′ : 4′ : 6′-*Tetrachlorobenzanilide and Dimethyl* αα′-*Azoisobutyrate.*—A solution of the *N*-chloroanilide (purity 96%; 20·8 g.) and the azo-ester (15·0 g.) in dry benzene was refluxed for 2·5 hr. ($CaCl_2$ guard-tube), the initial decomposition of the azo-ester being carried out with caution. The solvent was removed and the residual dark red tar was treated with light petroleum (b. p. 40—60°; 150 ml.). The extract was decanted and fractionated, yielding (i) methyl α-chloro*iso*butyrate (3·25 g., 41% calc. on the chloroanilide), b. p. 46·5—51°/34—40 mm. (amide, m. p. and mixed m. p. 119—121°) and (ii) a fraction, b. p. 82—100°/10 mm., which contained benzoyl chloride, for, on treatment with aniline, benzanilide, m. p. and mixed m. p. 162°, was obtained. In another experiment, quantitative hydrolysis of fraction (ii) indicated that the yield of benzoyl chloride was 35% (calc. on the chloroanilide). After the distillation there remained an involatile residue (10·7 g.). The red tar remaining after the treatment of the reaction product with light petroleum was diluted with benzene–light petroleum (b. p. 80—100°) and filtered. Chromatography of the filtrate yielded 3 : 5-*dichloro*-1 : 4-*benzoquinone* 1-(2 : 4 : 6-*trichloroanil*) (V) (0·4 g., 4%) which crystallised from alcohol in long purplish-red needles, m. p. 143° (Found: C, 40·9; H, 1·3; N, 4·1; Cl, 49·5. $C_{12}H_4ONCl_5$ requires C, 40·5; H, 1·1; N, 3·9; Cl, 49·9%).

Reaction between s-*Trichloroaniline and* 2 : 6-*Dichloro*-1 : 4-*benzoquinone.*—(i) To a solution of the amine in warm alcohol was added a hot solution of an equivalent amount of the quinone in the same solvent. The pale red solution was filtered and concentrated, yielding the *addition compound*, m. p. 80·5°, which formed black needles with a green reflex (Found: Cl, 47·2. $C_6H_2O_2Cl_2.C_6H_4NCl_3$ requires Cl, 47·4%). Attempted recrystallisation led to partial decomposition. (ii) Equivalent amounts of the amine and the quinone were refluxed together in glacial acetic acid; a pale brown solution was obtained, but on addition of a few drops of concentrated sulphuric acid, a purplish-red colour developed. After the whole had been refluxed for 0·5 hr., it was poured on ice, neutralised, and extracted with benzene. The dried extract, diluted with an equal volume of light petroleum (b. p. 80—100°), was chromatographed on alumina. Unchanged quinone passed rapidly through; elution of the more strongly absorbed band gave a dark red gum, whence a small quantity of the required quinone anil was obtained by repeated

crystallisation from alcohol; it had m. p. 142·5°, undepressed in admixture with the specimen obtained previously.

The work was carried out during the consecutive tenure by one of us (M. C. F.) of a Courtaulds' Senior Scholarship and an I.C.I. Research Fellowship. We also thank Imperial Chemical Industries Limited, Blackley, for generous gifts of αα'-azo*iso*butyronitrile.

THE DYSON PERRINS LABORATORY, OXFORD. [*Received, July 13th*, 1953.]

710. *Wool Wax. Part IV.* The Constitution of the Aliphatic Diols.*

By D. H. S. HORN and F. W. HOUGEN.

Five alkane-1 : 2-diols have been isolated from the unsaponifiable fraction of wool wax by chromatography and distillation at reduced pressure. They are identified, from infra-red studies and by degradation to fatty acids of known constitution, as *n*-hexadecane-, 16-methylheptadecane-, 18-methylnonadecane-, 20-methylheneicosane-, and 22-methyltricosane-1 : 2-diol.

KUWATA and KATUNO (*J. Soc. Chem. Ind. Japan, Suppl.*, 1938, **41**, 227) isolated from the unsaponifiable fraction of wool wax a dihydric alcohol, m. p. 79—80°, for which they proposed the formula $C_{21}H_{40}(OH)_2$. During a chromatographic study of the unsaponifiable fraction of wool wax on activated alumina, we isolated a similar material from the most strongly adsorbed fraction. However, attempts to purify it revealed that it was a complex mixture of closely related compounds, differing principally in molecular weight.

Oxidation with lead tetra-acetate yielded formaldehyde, characterised as its dimedone compound, and a mixture of aliphatic aldehydes which was readily converted, on mild oxidation, into the corresponding saturated fatty acids. These preliminary investigations established the main components as alkane-1 : 2-diols (Horn and Hougen, *Chem. and Ind.*, 1951, 670). Murray and Schönfeld later (*J. Amer. Oil Chem. Soc.*, 1952, **29**, 416) also reported the isolation of some diol fractions.

Initially, the diols were prepared in 2% yield from commercial wool wax unsaponifiables ("Hartolan," Messrs. Croda Ltd.). Subsequently, they were obtained in 4—5% yield from the unsaponifiable material prepared from wool wax extracted with *iso*heptane from merino wool, kindly supplied by the Director of the Grootfontein College of Agriculture and Experiment Station. To avoid the production of artefacts (Daniel, Lederer, and Velluz, *Bull. Soc. Chim. biol.*, 1945, **27**, 218), saponification of the wax was carried out at 40°. The unsaponifiable material was separated, almost quantitatively, by a method similar to that of Barnes, Curtis, and Hatt (*Austral. J. Appl. Sci.*, 1952, **3**, 88).

After the failure of attempts to resolve the diol mixture by fractional crystallisation and chromatography, the acetylated material was fractionally distilled at reduced pressure in a spinning-band microstill. In the initial stages of the work, the acetylated mixture was distilled without a break (Fig. 1). Later, with more material available, it was more profitable to fractionate it roughly at a low reflux ratio into several arbitrary fractions, redistil each fraction more thoroughly, and combine appropriate distillates. In this way, decomposition was reduced to a minimum. Finally, the main components were separately distilled. This lengthy procedure was necessary because chromatography and crystallisation failed to remove completely the long-chain alcohols, the presence of which greatly complicated the separation of, especially, the higher components (see Fig. 1) and made it impossible to calculate accurately the relative proportions of the diols present.

The following pure diols were obtained by saponification and crystallisation of the pure fractions: *n*-hexadecane-, 16-methylheptadecane-, 18-methylnonadecane-, 20-methylheneicosane-, and 22-methyltricosane-1 : 2-diol. No other diols could be detected: if present, they occurred only in very small amounts and were lost in the intermediate fractions or did not survive the lengthy distillation.

The structures of the individual diols were determined by direct oxidation with an excess

* Part III, *J.*, 1953, 98.

of lead tetra-acetate in a stream of air (cf. Mendel and Coops, *Rec. Trav. chim.*, 1939, **58**, 1140) to the corresponding fatty acids having one methylene group less than the parent diols. The acids produced were compared with synthetically prepared acids of known structure.

(±)-*n*-Octadecane-1 : 2-diol required for comparison was synthesised from 1-octadecene (Wibaut, *Rec. Trav. chim.*, 1948, **67**, 113; cf. Minoru *et al.*, *J. Chem. Soc. Japan*, 1949, **52**, 50; *Chem. Abs.*, 1951, **45**, 4635) by a modification of the method of Swern, Billen, and Scanlan (*J. Amer. Chem. Soc.*, 1946, **68**, 1505).

The structures of the pure diols were further confirmed by making use of Thompson and Torkington's observation (*Trans. Faraday Soc.*, 1945, **41**, 246; cf. Sobotka and Stynler, *J. Amer. Chem. Soc.*, 1950, **72**, 5139; Freeman, *ibid.*, 1952, **74**, 2526) that a doublet in the 1360—1400-cm.$^{-1}$ range of the infra-red absorption spectra of alkanes is characteristic of the *iso*propyl group. Hexadecane-1 : 2-diol showed a single absorption band, identical with that of synthetic (±)-octadecane-1 : 2-diol (Fig. 2), at 1380 cm.$^{-1}$. The other pure wool wax diols showed the characteristic splitting of the 1380 cm.$^{-1}$ band (Fig. 2), and the intensity of absorption was that expected for a single methyl branch.

FIG. 1. *Distillation curve.*

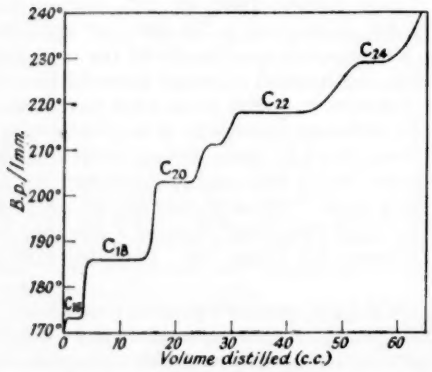
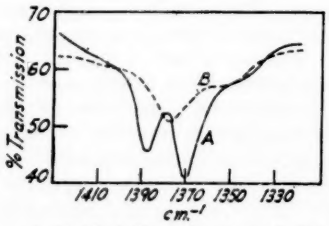


FIG. 2. *Infra-red absorption.*



A, 16-*Methylheptadecane*-1 : 2-*diol*.
B, *Octadecane*-1 : 2-*diol*.

The optical rotations of the pure diols could not be obtained with certainty because of their low solubilities. However, in contrast to (±)-octadecane-1 : 2-diol, they formed well-defined crystals and their diacetates had a slight dextrorotation. They have been correlated configurationally with the lævorotatory hydroxy-acids which occur in the wool-wax acid fraction (Horn, Hougen, and von Rudloff, *Chem. and Ind.*, 1953, 106). Thus on reduction with lithium aluminium hydride (−)-*n*-2-hydroxyhexadecanoic acid * and (−)-2-hydroxy-16-methylheptadecanoic acid yielded diols, respectively identical with *n*-hexadecane-1 : 2-diol and 16-methylheptadecane-1 : 2-diol obtained from the unsaponifiable material.

EXPERIMENTAL

Crystal long spacings were measured as described previously (Part III, *loc. cit.*). M. p. determinations were made with a heating rate of 3—4 min./degree in a " Hershberg "-type apparatus. Standardised, 8-cm., immersion thermometers were used.

The infra-red absorption spectra were obtained with the Perkin–Elmer spectrophotometer model 12C. An approx. 2% solution of the diol in carbon tetrachloride was run into a 0·5-mm. rock-salt cell warmed with an infra-red lamp. In this way, the diol could be kept in solution long enough after the lamp had been switched off to allow the absorption curve to be obtained.

Extraction of Wool Wax from Merino Fleeces.—Wool (2—3 kg.) was dried for 16 hr. at 60—70°/14—20 mm., and extracted for 7 hr. with *iso*heptane in a stainless-steel hot extractor. After storage for several days, the cold extract was decanted from the sludge and evaporated to dryness. In this way, 33·61 kg. of dried wool yielded 4·975 kg. (14·8%) of wool wax.

* Genera numbering, CO_2H = 1.

Saponification and Isolation of the Unsaponifiable Material.—To a mixture of wool wax (500 g.) and hexane (500 c.c.), at 40°, was added, with stirring, a solution of potassium hydroxide (85 g.) in ethanol (1 l. of 96%). The mixture was stirred at 40° for 24 hr. To the saponified mixture was added ethanol (660 c.c.) and water (1000 c.c.). The solution was shaken three times in a separating funnel (10 l.) with *n*-hexane. The combined hexane extracts, after being kept overnight in a tall cylindrical separating funnel, were separated from the sediment and shaken with 60% ethanol (2 × 500 c.c.). Evaporation of the hexane solution yielded extract I (131 g.).

The above alcohol solutions were combined and extracted in a continuous liquid–liquid extractor with hexane for 24 hr. The hexane extract was washed with 60% ethanol (200 c.c.) and evaporated to yield extract II (59 g.). The alcoholic wash-liquors were added to the next batch of saponified wax. The total yield of unsaponifiable material (extracts I and II) was 190 g. (38% of the wax).

Chromatographic Preparation of the Diols.—The wool-wax unsaponifiable material (500 g.), dissolved in wet ether (8 l., saturated with water at 6°), was filtered through a column of alumna (Peter Spence, type H), reactivated by 24 hr.' heating, with occasional stirring, at 400° (5 kg.; 30-cm. in height). The column was eluted with wet ether (24 l.), followed by ether (20 l.) containing ethanol (1% of 75%). The eluate was collected in 2-l. fractions. Those containing the material most strongly adsorbed were analysed by Karnovsky and Rapson's periodate titration method (*J. Soc. Chem. Ind.*, 1946, **65**, 138), and those containing considerable quantities of diols were amalgamated.

In this way, a crude diol fraction (186 g.) was obtained from the unsaponifiable material (2·2 kg.). It crystallised from ether and ethanol as a white powder (107 g.). The mother-liquors and fractions containing low diol contents (200 g.) were combined and rechromatographed. The crude diol fraction so obtained after crystallisation yielded further diol (30 g.). The total yield of crude diols (137 g.) was 6·2% of the unsaponifiable material.

To separate the diols from long-chain alcohols and other impurities, they were acetylated and distilled at 1 mm. in several batches in an electrically heated and vacuum-jacketed fractionating column (12 mm. internal diam.; 20 cm. long) packed with $\frac{1}{8}''$ Dixon gauze rings at a reflux ratio of about 1 : 10. The fractions of similar b. p. and n were combined to form the four following fractions: (1) b. p. 190—200°, n_D^{30} 1·4445, 54 c.c.; (2) b. p. 220—225°, n_D^{30} 1·4510, 37 c.c.; (3) b. p. 225—250°, solid, 32 c.c.; (4) b. p. 250—290°, n_D^{30} 1·4500—1·151, 59 c.c.

Fractions 1, 2, and 3 were separately saponified and crystallised from ether. Fraction 4, which contained the bulk of the high-boiling alcohols, was saponified and rechromatographed and the diol fraction crystallised. The material, obtained from the mother-liquors after crystallisation of the diols (fractions 1, 2, 3, and 4), was chromatographed and the diol fraction was obtained by crystallisation. A total of 90 g. of purified diols was obtained (4% yield). The above five diols fractions were separately acetylated and distilled. Distillates of similar b. p. were combined and redistilled where necessary.

The distillation was carried out in the microspinning band fractionating column of Piros and Glover (U.S. Pat. 2,608,528; *Chem. Abs.*, 1952, **46**, 9899; supplied by Messrs. H. S. Martin and Co., Illinois, U.S.A.) after modification as follows: (1) The pot heater, because of poor heat transfer, was replaced by two separately controlled heaters, one for the pot and the other for the exposed part of the column above the pot. (2) The column heater, because of uneven heating, was replaced by two evenly wound spiral heating elements. This allowed a better control over the temperature gradient in the column. (3) The partial condenser was replaced with a hollow centrally placed cold-finger condenser, which was fashioned at the end in the shape of hollow cone drawn down at one side to form a dripper. With this device it was possible, by comparison of the drop rate from this condenser with that from the dripper at the base of the column, to maintain a fine control over the column equilibrium. (4) The receiver was replaced by an electrically warmed one of the Perkin triangle type, which could be evacuated by means of a separate vacuum pump in order to avoid disturbing the column pressure. This type of still has a relatively low hold-up and low pressure drop and is thus suited to the fractionation of small quantities of not highly stable materials. The column temperatures were measured by means of iron–constantan thermocouples and recorded on a recording potentiometer (Messrs. Brown Instrument Co., Philadelphia, U.S.A.). The manostat of Birch *et al.* (*J. Soc. Chem. Ind.*, 1947, **66**, 3340) was used to maintain a pressure of 1 mm. with a maximum variation of about 0·02 mm. or a head-temperature variation of ≯ about 0·25°.

For the distillation, the column was operated at a boil-up rate of 30—40 c.c./hr., pressure drop of 1·2—1·5 mm., and rotor speed of 1200 r.p.m. Under these conditions of operation, it

had an efficiency of about 15 theoretical plates when tested with Williams's mixture (*Ind. Eng. Chem.*, 1947, **39**, 779). This is much lower than that claimed by the makers for operation at atmospheric pressure (*viz.*, 100 theor. plates). It is possible that the value is low because this test mixture does not wet glass well (cf. Benner, Dinardo, and Tobin, *Ind. Eng. Chem.*, 1951, **43**, 722; and Williamson, *J. Appl. Chem.*, 1951, **1**, 33). Comparison of our distillation curves with those of Murray (*J. Amer. Oil Chem. Soc.*, 1951, **28**, 1) suggests that our column is of roughly equal efficiency.

Isolation of the Pure 1 : 2-*Diols.*—n-*Hexadecane*-1 - 2-*diol.* A portion of the material from the C_{16} plateau (b. p. 173°/1 mm.) was saponified with alcoholic potasium hydroxide. Water was added and the diol, extracted with ether, was washed with water and dried (Na_2SO_4). After removal of the ether, the remaining *diol* was crystallised to purity from hexane and methanol, forming plates, m. p. 84—84·4°, crystal long spacing 36·7 Å (Found : C, 74·4; H, 13·4%; *M*, 261. $C_{16}H_{34}O_2$ requires C, 74·4; H, 13·3%; *M*, 258).

The molecular weight was determined by the volumetric method of Karnovsky and Rapson (*loc. cit.*). The m. p. was not depressed on admixture with an authentic sample of hexadecane-1 : 2-diol, m. p. 84—84·4°, prepared from (−)-*n*-2-hydroxyhexadecanoic acid by reduction with lithium aluminium hydride (Horn, Hougen, and von Rudloff, *Chem. and Ind., loc. cit.*).

n-*Pentadecanoic acid.* To hexadecane-1 : 2-diol (1 g.) in dry benzene at 50—60° was added slowly a solution of lead tetra-acetate (4 g.; Mendel, *Rec. Trav. chim.*, 1940, **59**, 720) in dry benzene (100 c.c.) and acetic acid (a few drops). A stream of air was passed through the mixture during the addition, and for 2 hr. thereafter. The mixture was then poured into an equal volume of dilute sulphuric acid, shaken, and centrifuged. The benzene layer was extracted several times with concentrated sodium hydroxide solution. The combined aqueous layers were extracted with ether, and acidified, and the liberated acid was taken up in ether. The ethereal solution was washed with water, dried (Na_2SO_4) and evaporated. The acid crystallised from pentane in plates, m. p. 52—52·2° (0·75 g.) (Found : C, 74·1; H, 12·6%; equiv., 242. Calc. for $C_{15}H_{30}O_2$: C, 74·3; H, 12·5%; equiv., 242·4). There was no m. p. depression on admixture with an authentic sample of pentadecanoic acid prepared from (±)-*n*-2-hydroxyhexadecanoic acid (Mendel and Coops, *Rec. Trav. chim.*, 1939, **58**, 1140), m. p. 52·2—52·5° (Found: C, 74·5; H, 12·7%; equiv., 243). Francis, Piper, and Malkin (*Proc. Roy. Soc.*, 1930, **128**, *A*, 214) record m. p. 52·1°.

1 : 2-*Diacetoxy*-16-*methylheptadecane.* The *diacetate* from the C_{18} plateau (b. p. 186·5°/1 mm.) crystallised from methanol at −20° as needles, m. p. 16—17°, $[\alpha]_D^{20} = +0{\cdot}012°$ (no solvent) (Found : C, 71·2; H, 11·6; Ac, 23·1. $C_{22}H_{42}O_4$ requires C, 71·3; H, 11·4; 2Ac, 23·2%).

16-*Methylheptadecane*-1 : 2-*diol.* 1 : 2-Diacetoxy-16-methylheptadecane was saponified and the *diol* crystallised from methanol and hexane as plates m. p. 75—75·4°, crystal long spacing 40·6 Å (Found : C, 75·8; H, 13·4%; *M*, 288. $C_{18}H_{38}O_2$ requires C, 75·5; H, 13·4%; *M*, 287). It showed no m. p. depression on admixture with 16-methylheptadecane-1 : 2-diol obtained by lithium aluminium anhydride reduction of (−)-16-methyl-2-hydroxyheptadecanoic acid (Horn, Hougen, and von Rudloff, unpublished work).

15-*Methylhexadecanoic acid.* 16-Methylheptadecane-1 : 2-diol was oxidised with lead tetra-acetate as described above. The acid was crystallised to purity from acetone, hexane, and methanol, forming plates, m. p. 60·1—60·5°, crystal long spacing 33·3 Å (Ställberg, Stenhagen, *et al., Arkiv Kemi, Min., Geol.*, 1948, **26**, *A*, No. 19, give 33·35 Å) (Found : C, 75·6; H, 12·7%; equiv., 271. Calc. for $C_{17}H_{34}O_2$: C, 75·5; H, 12·7%; equiv., 270). The m. p. showed no depression on admixture with an authentic specimen of 15-methylhexadecanoic acid, m. p. 60·3—60·5° (*idem, ibid.*).

1 : 2-*Diacetoxy*-18-*methylnonadecane.* The *diacetate* from the C_{20} plateau (b. p. 203°/1 mm.) crystallised from methanol as needles, m. p. 26—27° (Found : C, 72·6; H, 11·7; Ac, 21·9. $C_{24}H_{46}O_4$ requires C, 72·3; H, 11·6; Ac, 21·6%).

18-*Methylnonadecane*-1 : 2-*diol.* The foregoing diacetate was saponified. The *diol* crystallised from hexane and methanol as plates, m. p. 80·8—81·1°, crystal long spacing 44·5 Å (Found : C, 76·6; H, 13·6%; *M*, 322. $C_{20}H_{42}O_2$ requires C, 76·4; H, 13·5%; *M*, 315).

17-*Methyloctadecanoic acid.* 18-Methylnonadecane-1 : 2-diol was oxidised with lead tetra-acetate. The acid so obtained was crystallised to purity from hexane and acetone, giving plates, m. p. 66·6—66·8°, crystal long spacing 36·8 Å (Velick, *J. Amer. Chem. Soc.*, 1947, **69**, 2317, gives 36·2 Å) (Found : C, 76·5; H, 13·0%; equiv., 295. Calc. for $C_{19}H_{38}O_2$: C, 76·5; H, 12·8%; equiv., 298). The m. p. showed no depression on admixture with 17-methyloctadecanoic acid, m. p. 66·9—67·3°, kindly supplied by Prof. Cason.

1 : 2-*Diacetoxy*-20-*methylheneicosane.* The *diacetate*, b. p. 217—219°/1 mm., crystallised

from methanol as needles, m. p. 33·3—33·8° (Found: C, 73·2; H, 11·9; Ac, 20·4. $C_{26}H_{50}O_4$ requires C, 73·2; H, 11·8; Ac, 20·2%).

20-*Methylheneicosane*-1 : 2-*diol*. The foregoing diacetate was saponified. The *diol* crystallised from hexane and methanol as plates, m. p. 84·0—84·4°, crystal long spacing 48·6 Å (Found: C, 77·1; H, 13·6%; *M*, 342. $C_{22}H_{46}O_2$ requires C, 77·1; H, 13·5%; *M*, 343).

Synthesis of 19-*methyleicosanoic acid*. 18-Methylnonadecanoic acid (Part III, *loc. cit.*), reduced with lithium aluminium hydride in the usual way, yielded 18-methylnonadecanol, plates (from acetone and hexane), m. p. 50—50·3° (Found: C, 80·5; H, 14·4. Calc. for $C_{20}H_{42}O$: C, 80·5; H, 14·2%). Murray and Schoenfeld (*J. Amer. Oil Chem. Soc.*, 1952, **29**, 416) record m. p. 50·3° for 18-methylnonadecanol obtained from wool wax.

18-Methylnonadecanol (4 g.), iodine (2 g.), and red phosphorus (0·16 g.) were heated for 5 hr. at 145—150° with occasional shaking. An ethereal extract of the mixture was then washed free from acid, dried ($CaCl_2$), and evaporated, to yield 18-methylnonadecyl iodide (5·3 g.), plates (from acetone), m. p. 41—43°. A solution of this (4·8 g.) and potassium cyanide (1·6 g.) in 90% ethanol (80 c.c.) was refluxed for 24 hr. Potassium hydroxide (10 g.) in water (10 c.c.) was then added and the solution refluxed for 100 hr. The mixture, after dilution with water, was extracted at 50° with hexane. The alcoholic layer was acidified with hydrochloric acid, boiled for 10 min. and then extracted with three portions of hexane at 50°. The combined hexane extracts were washed with hot water, dried (Na_2SO_4), and concentrated to 50 c.c. The 19-*methyleicosanoic acid* then crystallised as plates (2·9 g.). Recrystallised from acetone, it had m. p. 73—73·3°, crystal long spacing 40·2 Å (Found: C, 77·2; H, 13·2%; equiv., 326. $C_{21}H_{42}O_2$ requires C, 77·2; H, 13·0%; equiv., 327).

The acid obtained from 20-methylheneicosane-1 : 2-diol by oxidation with lead tetra-acetate, crystallised to purity from acetone and hexane, formed plates, m. p. and mixed m. p. 73—73·4°, crystal long spacing 40·4 Å (Found: C, 77·3; H, 12·9%; equiv., 325).

1 : 2-*Diacetoxy*-22-*methyltricosane*. The *diacetate*, b. p. 228—230°/1 mm., crystallised from methanol as needles, m. p. 37·5—38·5° (Found: C, 74·1; H, 12·0; Ac, 19. $C_{28}H_{54}O_4$ requires C, 74·0; H, 12·0; Ac, 18·9%).

22-*Methyltricosane*-1 : 2-*diol*. 1 : 2-Diacetoxy-22-methyltricosane was saponified and the *diol* crystallised from hexane and then methanol formed plates, m. p. 86·6—97°, crystal long spacing 52·3 Å (Found: C, 78·1; H, 13·6%; *M*, 360. $C_{24}H_{50}O_2$ requires C, 77·8; H, 13·6%; *M*, 371).

Synthesis of 21-*methyldocosanoic acid*. 18-Methylnonadecanoic acid (5·5 g., 0·0175 mole), ethyl hydrogen glutarate (4·4 g., 0·027 mole), and sodium (0·02 g., 0·0008 g. atom) were electrolysed, to yield 21-*methyldocosanoic acid* (0·75 g.), plates (from acetone and ethanol), m. p. 77·9—78·1°, crystal long spacing 43·9 Å (Found: C, 78·0; H, 13·2%; equiv., 353. $C_{23}H_{46}O_2$ requires C, 77·9; H, 13·1%; equiv., 355).

21-Methyldocosanoic acid, obtained from 22-methyltricosane-1 : 2-diol by oxidation with lead tetra-acetate and crystallised to purity from acetone and hexane, formed plates, m. p. and mixed m. p. 76—76·6°, crystal long spacing 43·9 Å (Found: C, 77·9; H, 13·0%; equiv., 354).

Octadec-1-*ene*. Octadecyl alcohol (27 g., 0·1 mole) and palmitic acid (30 g., 0·114 mole) were heated together at 240—260° until evolution of water had ceased (*ca.* 1 hr.), and then distilled (b. p. 350—360°/600 mm.). The crude octadecene was separated from the bulk of the palmitic acid by distillation at atmospheric pressure through a "Towers 10-plate" fractionating column, then fractionated in the spinning-band column, and the material of constant b. p. and refractive index was collected (8·8 g.; b. p. 129°/1 mm., n_D^{30} 1·4408 ± 0·0001. Cf. Wibaut, *Rec. Trav. chim.*, 1948, **67**, 113).

(±)-n-1 : 2-*Diacetoxyoctadecane*. The method of Swern, Billen, and Scanlan (*loc. cit.*) was modified as follows: To a slowly stirred mixture of octadec-1-ene (16·3 g.) and formic acid (155 c.c.; 98—100%) at room temperature was added hydrogen peroxide (9·9 g. of 30% hydrogen peroxide, *i.e.*, 30% excess). The mixture was heated at 40° with slow stirring for 20 hr. The excess of formic acid was taken off under reduced pressure and the residue refluxed with potassium hydroxide (25 g.) in ethanol (200 c.c.) for 1 hr. The mixture was evaporated to small volume under reduced pressure, diluted with water, and extracted with ether. The ethereal layer was washed with water, dried (Na_2SO_4), and evaporated. The residue crystallised from pentane, to yield the crude diol (14·3 g.; m. p. 78·5—80·5°). It was dissolved in acetic anhydride (50 c.c.) and heated on a water-bath for 5 hr. The excess of acetic anhydride was removed and the residue fractionated at 1 mm. in the spinning-band column. The material of constant b. p. and refractive index (b. p. 191·5° ± 0·5°, n_D^{30} 1·4419 ± 0·0001) crystallised from methanol in needles, m. p. 39·5—40°, after resolidification m. p. 41·8—42·8° (Found: C, 71·5; H, 11·6; Ac, 23·3. Calc. for $C_{22}H_{42}O_4$: C, 71·3; H, 11·4; Ac, 23·2%). Nie-

mann and Wagner (*J. Org. Chem.*, 1942, **7**, 227) record m. p. 40·0° for (±)-1 : 2-diacetoxyoctadecane.

(±)-*Octadecane*-1 : 2-*diol*. Pure (±)-1 : 2-diacetoxyoctadecane was saponified and the diol crystallised from methanol as a colourless powder, m. p. 81—81·8°, crystal long spacing 40·4 Å (Found : C, 75·6; H, 13·5%; *M*, 285. Calc. for $C_{18}H_{38}O_2$: C, 75·5; H, 13·4%; *M*, 287). Swern *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1505) record m. p. 80—81° and Niemann and Wagner (*loc. cit.*), m. p. 79·0—79·5° for (±)-octadecane-1 : 2-diol.

The authors thank Drs. W. S. Rapson and D. A. Sutton for many helpful discussions, Mr. F. W. G. Schöning for the microanalyses, Dr. J. N. van Niekerk and Mr. F. R. L. Schöning for the *X*-ray measurements, Mr. C. A. J. Hoeve for the infra-red absorption spectra, and Prof. Cason for a sample of 17-methyloctadecanoic acid. This paper is published by permission of the South African Council for Scientific and Industrial Research. Acknowledgment is made of support from the South African Wool Board.

National Chemical Research Laboratory,
South African Council for Scientific and Industrial Research,
Pretoria, South Africa. [*Received, June 15th*, 1953.]

---

711. *Studies with Dithizone. Part V.* A Comparison of Routes for the Synthesis of* [^{35}S]*Dithizones.*

By H. Irving and C. F. Bell.

Of various routes for the synthesis of [^{35}S]dithizones, the action of alkali hydrogen sulphide on 1 : 5-diaryl-3-chloroformazans † shows most promise. The action of bromine (one or more equivalents) on 1 : 5-diphenylformazan gives 3-bromo-1 : 5-di-*p*-bromophenylformazan, also obtained by the bromination of the di-*p*-bromophenylformazan. Di-*p*-bromophenylthiocarbazone ("dibromodithizone") has been prepared by two routes, purified, and characterised.

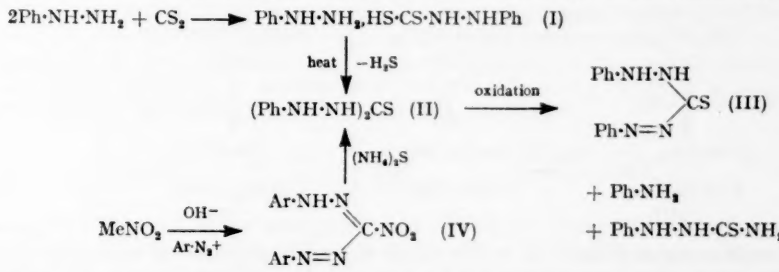
Studies of the physical chemistry of partition equilibria governing the extraction of traces of metals with diphenylthiocarbazone (III; "dithizone," HDz) have led us to consider the synthesis of this reagent "labelled" with a radioactive isotope (Irving, Bell, and Williams, *J.*, 1952, 357). This would facilitate its determination in either the aqueous or the organic phase whether present as the ion Dz^-, the undissociated molecule HDz, or as complexes $[MDz_m]^{n-m+}$ with an *n*-valent metal. Difficulties and limitations imposed by the customary absorptiometric determination of dithizone might thus be circumvented. In such work a prime consideration is to design the synthesis so as to minimise radiation hazards and to conserve valuable radioactive material. Since in the present paper we restrict ourselves to the introduction of radioactive sulphur, speed of working is of secondary importance and our conclusions would apply analogously to syntheses involving radiocarbon.

Three main synthetic routes to dithizone are available. The first (Fischer, *Annalen*, 1878, **190**, 120) involves the preparation of the phenylhydrazinium salt of β-phenylthiocarbazic acid (I) from phenylhydrazine and carbon disulphide, elimination of hydrogen sulphide by heating, and oxidation of the resulting diphenylthiocarbazide (II). The preparation of the salt (I) is practically quantitative and radio-sulphur could readily be introduced at this stage by use of $C^{35}S_2$; but in stage (I) to (II) half the activity would be lost in volatile products and although these can be recovered the thermal decomposition is not easy to control. The oxidation stage (II) to (III) as usually carried out with methylalcoholic potash involves self-oxidation and reduction in which only 25% at most of the original activity is retained. Although overall yields (based on the weight of phenylhydrazine taken) of 50—64% of crude dithizone have been claimed (*Org. Synth.*, **25**,

* Part III, *J.*, 1952, 356, Part IV, *J.*, 1952, 1216.

† The nomenclature is based on the Beilstein name "formazan" for $HN^1{:}N^2{\cdot}CH{:}N^3{\cdot}N^4H^5{:}_2$, numbered as shown.—Ed.

p. 28), the further stages of purification needed to prepare a sample suitable for spectrophotometric measurements (cf. Cooper and Sullivan, *Analyt. Chem.*, 1949, **23**, 613; Coope



and Kofron, *ibid.*, 1947, **21**, 1135; Sandell, "Colorimetric Determination of Traces of Metals," New York, 1950) may further reduce the yield by a factor of at least 10. We have attempted unsuccessfully to improve the yield in stage (II) to (III) by using other oxidising agents such as mercuric oxide or lead tetra-acetate in glacial acetic acid, and hydrogen peroxide under a variety of conditions.

A second route to dithizone, of special value for the synthesis of its analogues (Hubbard and Scott, *J. Amer. Chem. Soc.*, 1943, **65**, 2390; Oesper and Klingenberg, *J. Org. Chem.*, 1948, **13**, 309), starts with the preparation of a 1 : 5-diaryl-3-nitroformazan * (IV) by coupling an aryldiazonium salt with an alkaline solution of nitromethane. The reduction stage (IV) to (II) is carried out in rather variable yield by using an excess of ammonium sulphide (Bamberger, Padova, and Ormerod, *Annalen*, 1925, **446**, 260), and the final oxidation stage (II) to (III) is identical with Fischer's synthesis. Hubbard and Scott (*loc. cit.*) claim to have obtained 0·2 g. of purified di-β-naphthylthiocarbazone (as III) from 1 g. of the corresponding 1 : 5-diaryl-3-nitroformazan (as IV), but Coope and Kofron (*loc. cit.*), starting with 0·1 g. of material thus purified, found further purification necessary to get a product suitable for spectrophotometric work, their final yield being only 12 mg. From 1 g. of pure 1 : 5-di-*p*-bromophenyl-3-nitroformazan (as IV) we were unable to prepare more than 54 mg. of di-*p*-bromophenylthiocarbazone (as III) pure enough for spectrophotometry. Though more versatile than Fischer's synthesis, that of Bamberger *et al.* appears to present few advantages when over-all yields and general convenience are considered.

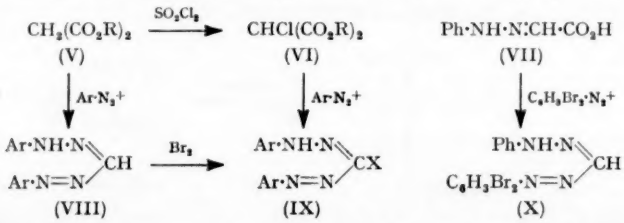
The third route exploits the reactivity of an ω-halogen atom in Ar·NH·N:CX·, and in the preparation of 3-bromo-1 : 5-diphenylformazan (IX; X = Br, Ar = Ph) for this purpose (see p. 3540) we were anticipated by Fusco and Romani (*Gazzetta*, 1946, **76**, 419, 439), who obtained dithizone by treating (IX; X = Cl, Ar′ = Ph) with sodium hydrogen sulphide, although full details are unknown. The necessary 3-chloroformazan is obtained by coupling a diazonium solution with dipotassium chloromalonate (VI; R = K), prepared from the chloro-ester (VI; R = Et) which results from the action of sulphuryl chloride on diethyl malonate (V; R = Et). Improvements in detail have enabled us to prepare the desired 3-chloro-1 : 5-diphenylformazan (as IX) pure and in good over-all yield. ω-Chlorodi-β-naphthylformazan (IX; X = Cl, Ar = β-$C_{10}H_7$), obtained similarly, formed a brown crystalline solid of constant m. p. 206—207° after only two recrystallizations from glacial acetic acid.

The conversion of 3-halogenoformazans into dithizones was investigated under a variety of conditions, 10 mg. of chlorodiphenylformazan being used in each case. The yield of pure product was determined by the absorptiometric method described on p. 3541. Typical results were :

Experimental conditions	Temp.	Yield, %
10 Min.' refluxing with excess of NaHS	78°	14·3, 12·0
10 Min.' mechanical shaking with excess of NaHS	18	39·8, 33·3
10 Min.' mechanical shaking with 1 equiv. of NaHS	18	8·4, 11·0

* See footnote on p. 3538 for nomenclature.

To avoid the troublesome preparation of the chlorodiphenylformazan, attempts were made to prepare the bromo-compound * (IX; X = Br, Ar = Ph) by direct bromination



of 1 : 5-diphenylformazan (VIII; Ar = Ph) which is readily prepared from malonic acid (V; R = H) and benzenediazonium chloride (Bamberger and Wheelwright, *Ber.*, 1892, **25**, 3201; von Pechmann and Runge, *Ber.*, 1894, **27**, 2920). With 1 equiv. of bromine the product was a tribromodiphenylformazan, m. p. 214—215°. This was obtained in better yield when 3 equivs. of bromine were used, but all attempts to prepare a less highly substituted product failed. The presence of a reactive 3-bromine atom was established by the ready reaction with sodium hydrogen sulphide to give a thiol closely resembling dithizone.

Phenylhydrazones of aromatic aldehydes generally brominate in the ω-position and in positions *ortho-* and *para-* to the nitrogen of the phenylhydrazine residue (cf. Chattaway, *J.*, 1930, 157), but the tribromodiphenylformazan was shown not to be identical with 3-bromo-1-(2 : 4-dibromophenyl)-5-phenylformazan prepared by the action of bromine on the 1-(2 : 4-dibromophenyl)-5-phenylformazan (X) obtained by the action of 2 : 4-dibromobenzenediazonium chloride on the phenylhydrazone (VII) of glyoxylic acid. Reduction of the tribromodiphenylformazan with stannous chloride in concentrated hydrochloric acid gave *p*-bromoaniline as the sole product and the formulation as 3-bromo-1 : 5-di-*p*-bromophenylformazan (IX; X = Br, Ar = *p*-C_6H_4Br) was established by its identity with the 3-bromination product of di-*p*-bromophenylformazan (VIII; Ar = *p*-C_6H_4Br), obtained by the action of *p*-bromobenzenediazonium chloride upon malonic acid.

The reactive halogen atom of 3-bromo-1 : 5-di-*p*-bromophenylformazan was readily replaced on 15 min.' refluxing in ethanol containing an equivalent amount of sodium hydrogen sulphide. Some reduction to the corresponding thiocarbazide occurred, but the expected di-*p*-bromophenylthiocarbazone ("dibromodithizone," as IX; X = SH, Ar = *p*-C_6H_4Br) was readily obtained by aerial oxidation and isolated after acidification as a blue-black solid, m. p. 145—147°. It closely resembles dithizone in its reactions, dissolving in ammonia or aqueous alkalis to give orange solutions and in organic solvents to give green solutions which give coloured complexes when shaken with aqueous solutions of zinc, lead, mercury, or silver. In carbon tetrachloride the absorption spectrum shows a principal maximum at 629 mμ (ε = 30,600) and a subsidiary maximum at 452 mμ. It closely resembles that of dithizone with maxima at 635 mμ (ε = 32,500) and 462 mμ. The expected similarity to dithizone throws doubt on the "dibromodithizone" prepared by Hubbard and Scott (*loc. cit.*) by reduction of 1 : 5-di-*p*-bromophenyl-3-nitroformazan (as IV) and described as a solid, m. p. 125°, like di-β-naphthylthiocarbazone insoluble in aqueous ammonia, and "possessing low tinctorial power." We have repeated Hubbard and Scott's preparation with some improvements in detail and obtained from 1 g. of the nitrophenylformazan 54 mg. of pure di-*p*-bromophenyldithiocarbazone identical in m. p. and absorption spectrum with the authentic specimen obtained from 3-bromo-1 : 5-di-*p*-bromophenylformazan.

Although the molecular extinction coefficient of dithizone or its analogues can be obtained directly by measuring the absorbancy of a suitably dilute solution of known concentration, yet any impurities in the sample will lead to spurious low values since the diarylthiocarbazones absorb more strongly in the visual region than their oxidation pro-

* In agreement with Fusco and Romani (*loc. cit.*, p. 429) we find that the action of an aryldiazonium solution on bromomalonic acid gives a halogen-free product.

ducts or structurally related substances. However, the mercury complexes are found to have negligible absorption at the long-wave maximum of the corresponding reagent, so that the absorbancy at this wave-length of a mixture of metal complex and free dithizone serves as a measure of the latter. Thus, if the initial absorbancy A_0 of v ml. of a dithizone solution of concentration c moles/l. is reduced to A_x after x μg. of mercuric ions (a deficiency) have been made to react quantitatively with it to give the complex of formula $HgDz_2$ (cf. Irving, Andrew, and Risdon, *J.*, 1949, 541), we have

$$A_0 = \varepsilon cl\,; \quad \varepsilon = 10^5 vl(A_0 - A_x)/x \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

and

$$c = A_0 x/10^5 vl(A_0 - A_x) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where l is the length of the optical cell used and ε is the molecular extinction coefficient of dithizone at the wave-length used. A linear plot of A_x against x for various amounts of mercury is used to obtain the slope $(A_0 - A_x)/x$, whence the extinction coefficient ε is calculated by equation (1). This procedure has been used for dithizone itself (Cooper and Sullivan, *loc. cit.*) but is capable of wider application. Conversely, knowing A_0, A_x, and x, we can determine the weight of pure dithizone in a solution of known volume from equation (2) without the need for the extensive purification and direct weighing of microgram samples. In this way the amount of pure material in samples which had been subjected to several stages of purification by extraction or crystallization could be determined, and typical overall yields are quoted below.

Dithiocarbazone formed	Starting material	Yield, %
Phenyl	3-Chloroformazan	39·8, 33·3
p-Bromophenyl	3-Bromoformazan	3·9
	Nitroformazan	5·6
β-Naphthyl	3-Chloroformazan	2·8
	Nitroformazan	2·5 [a]

[a] Following Scott and Hubbard (*loc. cit.*) and Coope and Kofron (*loc. cit.*). Percentages refer to spectrophotometrically pure material.

The direct synthesis of diarylthiocarbazides from thiocarbonyl chloride and phenylhydrazine (Heller, *Annalen*, 1891, **263**, 269) or bromo- or nitro-phenylhydrazines (Dyson, *J.*, 1937, 1358) eliminates the thermal decomposition stage (I) to (II) of Fischer's synthesis but the yields have not been investigated, since the preparation of $C^{35}S_2Cl_2$ would be exceedingly troublesome. All the syntheses proposed hitherto involve a stage of oxidation from thiocarbazide to thiocarbazone. Poor yields can generally be traced to loss of material or the introduction of by-products removable only with difficulty at this point. A direct synthesis from phenylthiosemicarbazide and nitrosobenzene failed. The most promising route to [^{35}S]diarylthiocarbazones appears to be through the 1 : 5-diaryl-3-chloroformazan, though, save for the diphenyl compound, the yields are poor. A practical disadvantage in the use of [^{35}S]dithizone is the weakness of the β-rays emitted which preclude the use of liquid counting.

Experimental

Preparation of 3-*Bromo*-1 : 5-*di*-p-*bromophenylformazan* (" *Tribromodiphenylformazan* ") (as IX; X = Br, Ar = *p*-C_6H_4Br).—(a) *By bromination of diphenylformazan.* Diphenylformazan (as VIII) (4·5 g., 1 mol.) in glacial acetic acid (25 ml.) was treated gradually with bromine (9·6 g., 2 mols.) in the cold. The mixture became warm and 3-*bromo*-1 : 5-*di*-p-*bromophenylformazan* separated immediately as a black solid. It was collected, washed with cold ethanol, and air-dried; after two recrystallizations from aqueous dioxan it formed minute orange crystals, m. p. 214—215° (Found: C, 33·6; H, 2·0; Br, 52·7; N, 12·1. $C_{13}H_9N_4Br_3$ requires C, 33·9; H, 2·0; Br, 52·0; N, 12·2%). A solution in concentrated hydrochloric acid (1 g. in 10 ml.) was boiled with stannous chloride (2 g.) till colourless. After the mixture had been made alkaline, *p*-bromoaniline was distilled in steam. The acetyl derivative (m. p. 167—168·5°; from water) and the benzoyl derivative (m. p. 202—203°) did not depress the m. p.s of authentic specimens.

(b) *By* ω-*bromination of* 1 : 5-*di*-p-*bromophenylformazan.* When a diazonium solution prepared from *p*-bromoaniline (35 g.) was added to a cooled aqueous solution of malonic acid (10·4 g.), 1 : 5-di-*p*-bromophenylformazan (as VIII; Ar = *p*-C_6H_4Br) separated as a dark red solid,

which was collected, dried, and recrystallized from aqueous dioxan (Found: N, 14·8; Br, 42·3. Calc. for $C_{13}H_{10}N_4Br_2$: N, 14·7; Br, 41·9%). The m. p. of our product, 177—178°, is much higher than that of Busch and Wolbring's preparation (114—115°; from aqueous acetic acid; *J. pr. Chem.*, 1905, **71**, 366). This may be due to polymorphism which is not uncommon among derivatives of diphenylformazan, although Hunter and Roberts (*J.*, 1941, 820) showed that for many cases of alleged " isomerism " in this series, differences of physical properties could usually be attributed to different degrees of purification. Complete elimination of the tarry by-products which have a profound influence on the m. p. is more readily effected with aqueous dioxan mixtures than with aqueous acetic acid mixtures.

When a solution of di-*p*-bromophenylformazan in glacial acetic acid was treated with bromine (1 equiv.) in the cold, 3-bromo-1 : 5-di-*p*-bromophenylformazan separated as a dark brown solid which after two recrystallizations from aqueous dioxan melted at 213—214° and did not depress the m. p. of the " tribromodiphenylformazan " described above.

Preparation of 1-(2 : 4-*Dibromophenyl*)-5-*phenylformazan* (X).—(i) The phenylhydrazone of glyoxylic acid (prepared by electrolytic reduction of a saturated aqueous solution of oxalic acid : cf. Tafel and Friedrichs, *Ber.*, 1900, **33**, 2209; 1904, **37**, 3188) had m. p. 136° (from aqueous ethanol) (Busch and Meussdörffer, *J. pr. Chem.*, 1907, **75**, 121 report 137°). This phenylhydrazone (VII; 2·25 g.) in water (50 ml.) containing sodium hydroxide (2 g.) was treated at 0° with a diazonium solution prepared from 2 : 4-dibromoaniline (3·94 g., 1 equiv.). 1-(2 : 4-*Dibromophenyl*)-5-*phenylformazan* (X), which separated, formed orange-red crystals, m. p. 198—200° after several crystallisations from benzene–acetone (Found: N, 14·6; Br, 41·7. $C_{13}H_{10}N_4Br_2$ requires N, 14·7; Br, 41·9%).

Bromination of (X) gave a product, m. p. 270°, which was not identical with the tribromination product from diphenylformazan. Owing to its insolubility in common solvents, this compound was not further investigated.

Preparation of 1 : 5-*Diaryl*-3-*chloroformazans*.—Diethyl malonate (50 g.) and sulphuryl chloride (45·6 g.) were heated under reflux for 1 hr. Fractionation gave diethyl chloromalonate (VI; R = Et), b. p. 113°/10 mm. This chloro-ester (25 g.) in ethyl alcohol (30 ml.) was treated in the cold with a solution of potassium hydroxide (16·6 g.) in ethyl alcohol (70 ml.). Potassium chloromalonate (VI; R = K) rapidly separated. It was collected and washed well with alcohol, and all traces of solvent were removed by keeping the solid salt under vacuum for several days. Potassium chloromalonate (22 g.) in water (100 ml.) containing sodium acetate (40 g.) was treated at 0° (mechanical stirrer) with a diazonium solution prepared from 27 g. of aniline hydrochloride. A dark red, granular precipitate slowly separated, and after being kept overnight this was collected and dried. Recrystallization from ethanol gave 3-chloro-1 : 5-diphenylformazan as dark red needles, m. p. 150—151° (Fusco and Romani, *loc. cit.*, report 153°). Complete removal of alcohol from the potassium chloromalonate before coupling increased the yield by reducing the amount of tarry by-products obtained when Fusco and Romani's preparative details are followed.

3-Chloro-1 : 5-di-β-naphthylformazan (25 g., 70%) was prepared similarly from potassium chloromalonate (21·4 g.) and a diazonium solution from β-naphthylamine (31·5 g.). It formed dark brown crystals, m. p. 206—207°, from acetic acid (Fusco and Romani give 213—214°).

Preparation of Di-p-*bromophenylthiocarbazone*.—(a) *From* 3-*bromo*-1 : 5-*di*-p-*bromophenylformazan*. A solution of sodium hydrogen sulphide, prepared by saturating a solution of sodium (0·023 g.) in ethyl alcohol (10 ml.) with dry hydrogen sulphide, was refluxed for 15 min. with " tribromodiphenylformazan " (0·46 g.). The initial orange colour became pale green, and after the mixture had cooled air was drawn through it until the rapid colour change to deep orange indicated the formation of the sodium salt of the expected thiocarbazone. On addition of excess of dilute hydrochloric acid di-*p*-bromophenylthiocarbazone separated as an almost black solid. The crude material (0·5 g.) was dissolved in carbon tetrachloride (50 ml.) and shaken with a mixture of ammonia (*d* 0·88; 50 ml.) and doubly-distilled water (450 ml.). Most of the dibromodithizone passed into the aqueous phase as the orange-coloured ion. The organic phase was rejected, and the aqueous solution washed with three successive portions of carbon tetrachloride (20 ml.). The aqueous extract was then kept at 0—5° while being cautiously made acid, and the dibromodithizone which then separated was dissolved in pure chloroform (20—30 ml.) and transferred to a beaker placed in a vacuum desiccator which contained calcium chloride and a small heating coil. The latter was used to maintain a temperature of about 25° while the solvent was evaporated under greatly reduced pressure. Completely dry *di*-p-*bromophenylthiocarbazone* which remained could be further purified by dissolving it in a small volume of pure chloroform and adding light petroleum. It formed bluish-black crystals with a

coppery reflex, m. p. 145—147° (Found: C, 37·5; H, 2·5; Br, 38·7. $C_{13}H_{10}N_4Br_2S$ requires C, 37·7; H, 2·4; Br, 38·6%).

(b) *From* 1 : 5-*di*-p-*bromophenyl*-3-*nitroformazan*.—The 1 : 5-diarylnitroformazan (1 g., m. p. 156—158°; cf. Hubbard and Scott, *loc. cit.*) was suspended in ethyl alcohol (25 ml.) and saturated alternately with ammonia and hydrogen sulphide until the completion of the reduction was shown by the change of colour from red to yellow and by the disappearance of particles of starting material. No attempt was made to isolate the product, but 10 ml. of 5% alcoholic potassium hydroxide were added, and the mixture heated for a few minutes, a deep orange colour then being seen. The mixture was cooled and acidified; dibromodithizone separated and was purified as previously described. The yield of pure material, m. p. 146—148°, was 0·056 g.

The Molecular Extinction Coefficient of Di-p-*bromophenylthiocarbazone*.—10 ml. of a dilute solution of the purest dibromodithizone available (~6·5 mg./l.) in carbon tetrachloride were equilibrated with 10 ml. of a solution of x μg. of mercuric ion in 0·1N-sulphuric acid. The absorbancy (1-cm. cell) at 635 mμ was measured with a Beckman Model DU spectrophotometer. For the linear plot of absorbancy against x a slope of 0·0306 per μg. of Hg^{++} was found, whence $\varepsilon = 30{,}600$. This checks absolutely with the value calculated from the absorbancy (0·825) of a solution in carbon tetrachloride containing 11·16 mg./l. In this solvent $\lambda_{min.} = 525$ mμ ($\varepsilon_{min.} = 7{,}200$) and the subsidiary $\lambda_{max.} = 463$ mμ ($\varepsilon = 20{,}030$).

Grateful acknowledgment is made to the Department of Scientific and Industrial Research for a maintenance grant to one of us (C. F. B.) and to Imperial Chemical Industries Limited for the loan of a Beckman spectrophotometer.

INORGANIC CHEMISTRY LABORATORY,
SOUTH PARKS ROAD, OXFORD.

[*Received, June 19th,* 1953.]

---

712. *The Structures of Some Monoquaternary Salts of 5-Substituted 4 : 7-Phenanthrolines.*

By W. O. SYKES.

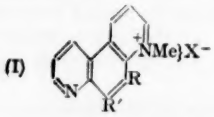
The methiodide prepared directly from 5-chloro-4 : 7-phenanthroline is shown to be the 7-methiodide, isomeric with the 5-chloro-4-methyl-4 : 7-phenanthrolinium iodide synthesised from a quaternary salt of 6-acetamido-8-chloroquinoline by means of a Skraup reaction. The methiodides of 5-acetamido-, 5-bromo-, and 5-chloro-4 : 7-phenanthroline, prepared directly, are converted in simple steps into the same compound, 5-amino-7 : 8-dihydro-7-methyl-8-oxo-4 : 7-phenanthroline; therefore the reaction of methyl iodide with either 5-acetamido- or 5-bromo-phenanthroline, as with the 5-chloro-compound, produces a 5-substituted 7-methiodide.

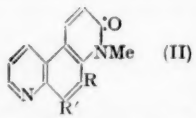
THE main object of the present work was to identify the products of direct quaternisation of certain 5-substituted 4 : 7-phenanthrolines. Both 5-acetamido- and 5-bromo-4 : 7-phenanthroline give good yields of monomethiodides when heated with excess of methyl iodide in sealed tubes at 100° for 30 min. (Haworth and Sykes, *J.*, 1944, 311). In each case the product is a single compound, not a mixture of the 4- and the 7-methiodide (I; X = I, R′ = H; X = I, R = H, respectively; Ring Index numbering). A methiodide (*A*) of 5-chloro-4 : 7-phenanthroline was prepared by a method parallel to that described for the bromo-analogue; a Skraup reaction with 2-chloro-4-nitroaniline gave 8-chloro-6-nitroquinoline which was reduced with stannous chloride, and the resulting 6-amino-8-chloroquinoline in a second Skraup reaction gave 5-chloro-4 : 7-phenanthroline, which was quaternised in 80% yield with an excess of methyl iodide. The 5-chloro-4 : 7-phenanthroline was identified by oxidation with potassium permanganate in alkaline solution to 3 : 3′-dipyridyl-2 : 2′-dicarboxylic acid with the liberation of chloride ions, and by conversion into the known 5-amino-4 : 7-phenanthroline (Haworth and Sykes, *loc. cit.*).

A second methiodide (*B*) of 5-chloro-4 : 7-phenanthroline was obtained in 35% yield by precipitation with potassium iodide from the neutralised products of Skraup reactions

performed on the methiodide or, more conveniently, the methotoluene-*p*-sulphonate of 6-acetamido-8-chloroquinoline.

The methiodide (*B*) must be 5-chloro-4-methyl-4 : 7-phenanthrolinium iodide (I; X = I, R = Cl, R′ = H), and (*A*) must therefore be the 7-methiodide (I; X = I, R = H, R′ = Cl). Two lines of evidence showed that isomerisation did not take place during the Skraup reaction used to prepare the 4-methiodide: first, a 30% recovery of unchanged





7-methiodide alone was made after its subjection to the conditions of the Skraup reaction; secondly, a Skraup reaction performed on the crude product of alkaline ferricyanide oxidation of 6-acetamido-8-chloroquinoline methotoluene-*p*-sulphonate gave, although in very poor overall yield, the same dihydro-*N*-methyl-oxo-compound (II; R = Cl, R′ = H) as was obtained by oxidation of the methiodide (*A*). The two methiodides of chlorophenanthroline were oxidised by alkaline potassium ferricyanide to the corresponding dihydro-*N*-methyl-oxo-derivatives in about 70% yield, and these were shown to be isomeric by conversion into the same 5-chloro-3 : 4 : 7 : 8-tetrahydro-4 : 7-dimethyl-3 : 8-dioxo-4 : 7-phenanthroline by alkaline ferricyanide oxidation of their methiodides. 5-Chloro-7 : 8-dihydro-7-methyl-8-oxo-4 : 7-phenanthroline (II; R = H, R′ = Cl) was unaffected when heated for as long as 2 hr. with excess of methyl iodide at 100° but was quaternised by treatment with hot methyl toluene-*p*-sulphonate, whilst the 3 : 4-dihydro-4-methyl-3-oxo-compound (II; R = Cl, R′ = H) reacted readily with methyl iodide at 100°.

Unlike 8-chloroquinoline (Claus and Schöller, *J. pr. Chem.*, 1893, **48**, 144), 6-acetamido-8-chloroquinoline reacted very little, if at all, with methyl iodide at 100° (1 hr.). A quaternary salt was obtained in 70% yield by the action of methyl toluene-*p*-sulphonate at about 200°. The product was easily hydrolysed by hot mineral acid to the 6-amino-derivative. Alkaline ferricyanide oxidation of the quaternary salts of both 6-acetamido- and 6-amino-8-chloroquinoline gave very poor yields, and it was to avoid losses in working up that the crude product obtained from the 6-acetamido-salt was used in the above Skraup reaction.

The amino-dihydro-*N*-methyl-oxo-compounds (II; R = NH_2, R′ = H; and R = H, R′ = NH_2) were prepared by heating the corresponding chloro-bases with concentrated ammonia solution, phenol, and a trace of copper salt for 3 days at about 180° (B.P. 454,525). 5-Amino-7 : 8-dihydro-7-methyl-8-oxo-4 : 7-phenanthroline was also obtained when these conditions were applied to the dihydro-*N*-methyl-oxo-compound prepared from 5-bromo-4 : 7-phenanthroline methiodide, which was thus shown to be a 5-substituted 7-methiodide. Further, this amino-derivative was identical with the product obtained, although in very small yield, by alkaline ferricyanide oxidation of the directly prepared methiodide of 5-acetamido-4 : 7-phenanthroline and subsequent hydrolysis of the crude product; the acetamidophenanthroline methiodide is, therefore, yet another 5-substituted 7-methiodide.

5-Acetamido-4 : 7-phenanthroline was prepared from the amino-derivative obtained by replacement of the halogen atom in 5-bromo-4 : 7-phenanthroline (B.P. 454,525; Haworth and Sykes, *loc. cit.*) or, similarly but in rather smaller yield (about 30%), from 5-chloro-4 : 7-phenanthroline; the overall yields in the somewhat tedious preparations from the benzenoid precursors were in neither case good. Renewed attempts to prepare 5-nitro-4 : 7-phenanthroline and 4 : 7-phenanthroline-5-sulphonic acid in the hope of providing easier access to the aminophenanthroline were unsuccessful; further Skraup reactions (cf. Haworth and Sykes, *loc. cit.*) with 2 : 5-diaminonitrobenzene and 2 : 5-diaminobenzenesulphonic acid failed. The intention to prepare 4 : 7-phenanthrolinesulphonic acid in two stages was not accomplished; a Skraup reaction with 2-amino-5-nitrobenzenesulphonic acid yielded, not the expected 6-nitroquinoline-8-sulphonic acid, but 6-nitroquinoline, identical with the product of a Skraup reaction on *p*-nitroaniline. A similar desulphonation is reported to occur in the attempted preparations of two hydroxy-

quinolinesulphonic acids (Claus and Posselt, *J. pr. Chem.*, 1890, **41**, 32). From attempts at direct sulphonation of 4 : 7-phenanthroline in fuming sulphuric acid (50% w/w SO_3) for 35 hr. at 90° or 2 hr. at about 150° good recoveries of the unchanged base only were made : the latter conditions are similar to those stated to be effective for the sulphonation of 3-phenyl-4 : 7-phenanthroline (Willgerodt and Jablonski, *Ber.*, 1900, **33**, 2918).

There exists a long-standing claim for the preparation of 5-amino-3 : 4-dihydro-4-methyl-3-oxo-4 : 7-phenanthroline. Kaufmann and Radošević (*Ber.*, 1909, **42**, 2612) found that, unlike the parent base, 3 : 4-dihydro-4-methyl-3-oxo-4 : 7-phenanthroline was readily nitrated by mixed concentrated sulphuric and fuming nitric acids at 100° to a mononitro-derivative, and they assigned position 5 to the substituent without substantiating evidence; they reduced this compound to the amino-compound. A specimen of Kaufmann and Radošević's amino-derivative, prepared by their method with small modifications, was not identical with either of our 5-amino-dihydro-*N*-methyl-oxo-4 : 7-phenanthrolines, and the nitro-group cannot, therefore, have been introduced at either of the *Bz*-positions.

Experimental

8-Chloro-6-nitroquinoline.—A mixture of 2-chloro-4-nitroaniline (25 g.), water (70 c.c.), concentrated sulphuric acid (90 c.c.), glycerol (35 c.c.), and arsenic acid (40 c.c.; *d* 1·8) was boiled gently under reflux for 3 hr. The product was cooled, diluted to 1 l., filtered, and made alkaline with 40% sodium hydroxide solution, the mixture being kept cool by addition of ice. The precipitate was filtered off, washed, dried, and extracted with boiling benzene (300 c.c.); *8-chloro-6-nitroquinoline* (15 g.) crystallised from the extract when it was allowed to cool. Recrystallisation from benzene or alcohol (charcoal) gave yellow prisms or needles respectively, m. p. 154° (Found : Cl, 16·8. $C_9H_5O_2N_2Cl$ requires Cl, 17·0%).

6-Amino-8-chloroquinoline.—A solution of stannous chloride dihydrate (70 g.) in concentrated hydrochloric acid (50 c.c.) was added in small portions with stirring to a cooled solution of 8-chloro-6-nitroquinoline (20 g.) in concentrated hydrochloric acid (60 c.c.). The mixture was cooled thoroughly and the precipitated stannichloride was filtered off, dissolved in boiling water (600 c.c.), and poured with vigorous stirring into 20% sodium hydroxide solution (1—2 l.). After cooling, the precipitate was filtered off, washed, dried, and extracted with boiling dibutyl ether (600 c.c.) from which, when it was cooled, 6-amino-8-chloroquinoline (12 g.) separated. Recrystallisation of the product from dibutyl ether or benzene gave pale yellow leaflets, m. p. 153° [Hutchinson and Kermack (*J.*, 1947, 678), who used West's method, give m. p. 154° and quote Curd's product (unpublished method), m. p. 156—157°] (Found : Cl, 19·7. Calc. for $C_9H_7N_2Cl$: Cl, 19·9%). The *acetyl* derivative, prepared in almost quantitative yield by acetic anhydride–acetic acid on the water-bath (10—15 min.), crystallised from 10% acetic acid in clusters of threads, m. p. 196—197° (Found : C, 59·4; H, 4·2; N, 12·5; Cl, 15·8. $C_{11}H_9ON_2Cl$ requires C, 59·9; H, 4·1; N, 12·7; Cl, 16·1%).

6-Acetamido-8-chloro-1-methylquinolinium Toluene-p-sulphonate.—6-Acetamido-8-chloroquinoline (10 g.) was dissolved by stirring it into methyl toluene-*p*-sulphonate (100 g.) at about 120°. The mixture was heated during 10 min. to about 200°, and the dark red product, while still hot, was poured on to an equal weight of crushed ice. Unchanged ester was removed by extraction with ether (2 × 150 c.c.). The aqueous solution was mixed with cold, saturated ammonium sulphate solution (300 c.c.), and the precipitated solidifying oil was filtered off, washed with methanol, and dried (13 g.). The product crystallised from methanol in yellow prisms, m. p. about 227° with previous darkening and softening. That this product was the *methotoluene-p-sulphonate* and not a methosulphate was shown by its freedom from sulphate and ammonium ions, by the preparation from it of a specimen of toluene-*p*-sulphonamide after removal of the cation as its sparingly soluble iodide and then of excess of iodide with silver nitrate, and by its composition (Found : S, 8·2; Cl, 8·6. $C_{19}H_{19}O_4N_2SCl$ requires S, 7·9; Cl, 8·7%). The *methiodide* (4 g.) was deposited when potassium iodide (5 g.) in a little water was added to the methotoluene-*p*-sulphonate (5 g.) in water (50 c.c.); recrystallised from water it formed yellow prismatic needles, m. p. about 200° (decomp.) depending on the rate of heating, with previous softening (Found : I, 34·6. $C_{12}H_{12}ON_2ClI$ requires I, 35·0%).

6-Amino-8-chloro-1-methylquinolinium Iodide.—A solution of 6-acetamido-8-chloroquinoline methotoluene-*p*-sulphonate (3 g.) in 2N-hydrochloric acid (30 c.c.) was boiled under reflux for 1 hr., cooled, and neutralised to pH 6—7. Addition of potassium iodide (10 g.) in a little water gave an immediate yellow precipitate of *6-amino-8-chloroquinoline methiodide* (2·2 g.), golden-

yellow needles (from methanol), m. p. about 198° (decomp.) (Found: I, 39·2. $C_{10}H_{10}N_2ClI$ requires I, 39·6%).

6-Acetamido-8-chloro-1 : 2-dihydro-1-methyl-2-oxoquinoline.—To a cold solution of 6-acetamido-8-chloroquinoline methotoluene-*p*-sulphonate (4 g.) in water (100 c.c.), or an equivalent solution of the methiodide, was added 10% sodium hydroxide solution (15 c.c.), followed immediately by 10% potassium ferricyanide solution (80 c.c.), with stirring. After 30 min. the dark, turbid mixture was made strongly alkaline with 40% sodium hydroxide solution, and the sticky, solidifying precipitate was separated, air-dried (about 1 g.), and extracted with a small volume of chlorobenzene in a continuous extractor. The brown material which crystallised on cooling was recrystallised from methanol (charcoal), to produce pale yellow needles (0·1 g.) of the *oxo*-compound, m. p. 258—259° (Found: Cl, 14·4. $C_{12}H_{11}O_2N_3Cl$ requires Cl, 14·2%).

5-Chloro-4 : 7-phenanthroline.—6-Amino-8-chloroquinoline (10 g.), water (25 c.c.), concentrated sulphuric acid (25 c.c.), glycerol (15 c.c.), and crude sulphonated nitrobenzene (15 g.) were refluxed gently for 6 hr., then cooled, diluted to 250 c.c., and filtered. The filtrate was made strongly alkaline with ammonia solution (*d* 0·88) (ice-cooling) and kept overnight. The separated product was purified by conversion into the nitrate, which crystallised on cooling of a hot solution of the base in 2N-nitric acid (100 c.c.). The crude *chlorophenanthroline*, liberated by gradually basifying a paste of the nitrate with water, was dried (7 g.) and purified by distillation at 20 mm. and crystallisation from chlorobenzene–ligroin from which it formed colourless needles, m. p. 155° (Found: Cl, 16·3. $C_{12}H_7N_2Cl$ requires Cl, 16·5%). Oxidation of the chlorophenanthroline (2·1 g.) with alkaline potassium permanganate in alkaline solution, by Smith's procedure (*J. Amer. Chem. Soc.*, 1930, **52**, 397) for the unsubstituted base, gave 3 : 3′-dipyridyl-2 : 2′-dicarboxylic acid (0·5 g.), m. p. 210° (decomp.) alone or mixed with a specimen prepared from 4 : 7-phenanthroline. The *nitrate* of chlorophenanthroline on crystallisation from dilute nitric acid (charcoal) and then from water formed colourless threads, m. p. 256° (decomp.) (Found: equiv., 276. $C_{12}H_7N_2Cl,HNO_3$ requires equiv., 277·7).

5-Chloro-7-methyl-4 : 7-phenanthrolinium iodide (I; X = I, R = H, R′ = Cl) was obtained by heating the base (3 g.) with an excess of methyl iodide in a sealed tube in a boiling-water bath for 30 min. The orange product (4 g.), when washed with ether and crystallised from water, formed red prisms, m. p. 278° (decomp.) with previous darkening and softening (Found: I, 35·3. $C_{13}H_{10}N_2ClI$ requires I, 35·6%).

5-Chloro-4-methyl-4 : 7-phenanthrolinium Iodide (I; X = I, R = Cl, R′ = H).—6-Acetamido-8-chloroquinoline methotoluene-*p*-sulphonate (10 g.), water (12 c.c.), concentrated sulphuric acid (12 c.c.), glycerol (7 c.c.), and crude sulphonated nitrobenzene (7 g.) were boiled gently under reflux for 3 hr. and the product was cooled, diluted to 150 c.c., and neutralised to pH *ca.* 6 (ice-cooling). After separation from the precipitated tar and treatment with charcoal, the supernatant liquid was mixed with a solution of potassium iodide (50 g.) in a little water.

Deposition of the chlorophenanthroline *methiodide* was complete in about 30 min. The product (3 g.) crystallised from water as yellow prismatic needles, m. p. 272° (decomp.) with previous darkening and softening, sharp decomp. on rapid heating to > *ca.* 230° (Found: I, 35·4%). The methotoluene-*p*-sulphonate could be replaced by the methiodide, but iodine liberated immediately on mixing caused bumping; there was no nuclear iodination.

5-Chloro-7 : 8-dihydro-7-methyl-8-oxo-4 : 7-phenanthroline (II; R = H, R′ = Cl).—5-Chloro-4 : 7-phenanthroline 7-methiodide (4 g.) was oxidised with alkaline potassium ferricyanide (cf. Douglas, Jacomb, and Kermack, *J.*, 1947, 1659). The product precipitated by the final addition of alkali was dried and extracted with boiling chlorobenzene from which the *chloro-base* (2 g.) crystallised on cooling. Recrystallisation from benzene or chlorobenzene gave very pale yellow needles, m. p. 251° (Found: Cl, 14·4. $C_{13}H_9ON_2Cl$ requires Cl, 14·5%). The *methiodide* was prepared by heating the chloro-base (1 g.) briefly in methyl toluene-*p*-sulphonate (10 g.) solution, partitioning the cooled product between ether and water, and adding potassium iodide to the aqueous solution. The product (0·6 g.) crystallised from methanol in flocculent yellow threads, decomp. > *ca.* 200° leaving a residue of the original base (Found: I, 32·9. $C_{14}H_{12}ON_2ClI$ requires I, 32·8%).

5-Chloro-3 : 4-dihydro-4-methyl-3-oxo-4 : 7-phenanthroline (II; R = Cl, R′ = H).—5-Chloro-4 : 7-phenanthroline 4-methiodide (4 g.) was similarly oxidised with alkaline potassium ferricyanide. The *chloro-base* separated from the reaction mixture without the final addition of strong alkali, and was dried (2 g.) and crystallised from chlorobenzene or benzene in very pale yellow needles, m. p. 209° (Found: Cl, 14·3%). The same compound (0·05 g.) was obtained by a Skraup reaction from the crude oxidation product of 6-acetamido-8-chloroquinoline methiodide (2 g.), the proportions of reactants prescribed for the Skraup reaction on the methiod-

ide itself being used. The ***methiodide*** of (II; R = Cl, R′ = H) was obtained (1·4 g.) by heating the chloro-base (1 g.) with excess of methyl iodide at 100° for 30 min., and crystallised from water or methanol in orange needles, m. p. about 253° (decomp.) with previous darkening and softening (Found: I, 32·4%).

5-Bromo-7 : 8-dihydro-7-methyl-8-oxo-4 : 7-phenanthroline (II; R = H, R′ = Br).—The 7-methiodide (5 g.) prepared directly from 5-bromo-4 : 7-phenanthroline (Haworth and Sykes, *loc. cit.*) was oxidised with alkaline potassium ferricyanide by the procedure given above for the oxidation of the chloro-analogue. The *product*, which separated practically completely without the reaction mixture being made strongly alkaline, was washed with water and dried (3 g.); it crystallised from chlorobenzene or xylene in yellow needles, m. p. 278° (Found: Br, 27·8. $C_{13}H_9ON_2Br$ requires Br, 27·6%).

5-Chloro-3 : 4 : 7 : 8-tetrahydro-4 : 7-dimethyl-3 : 8-dioxo-4 : 7-phenanthroline was obtained by oxidation of the methiodides of both 5-chloro-dihydro-*N*-methyl-oxo-4 : 7-phenanthrolines with alkaline potassium ferricyanide. Much of it separated from the reaction mixtures without the final addition of strong alkali, was dried, and crystallised from formamide in thread-like needles, m. p. 326° with previous darkening and softening (Found: Cl, 12·5. $C_{14}H_{11}O_2N_2Cl$ requires Cl, 12·9%).

5-Amino-7 : 8-dihydro-7-methyl-8-oxo-4 : 7-phenanthroline (II; R = H, R′ = NH_2).—The chloro-base (II; R = H, R′ = Cl) (1 g.), phenol (1 g.), concentrated ammonia solution (3 c.c.), and a trace of copper acetate were heated for 3 days at about 180°. The product was washed from the tube with an excess of dilute sulphuric acid and the mixture was treated, while hot, with charcoal. The material precipitated from the cooled solution by basification with 40% sodium hydroxide solution was purified by conversion into the hydrochloride, sparingly soluble in cold dilute hydrochloric acid, and the re-liberated base was dried and extracted in a continuous extractor with a small volume of chlorobenzene. The *amino*-compound, which separated from the chlorobenzene during the extraction and on cooling the extract, was filtered off (0·3 g.) and crystallised from chlorobenzene in yellow needles, m. p. 296° with previous darkening and softening (Found: C, 69·2; H, 4·9; N, 18·5. $C_{13}H_{11}ON_3$ requires C, 69·3; H, 4·9; N, 18·7%). The same product was obtained in similar yield when the bromo-analogue (II; R = H, R′ = Br) was used in place of the chloro-base.

5-Acetamido-4 : 7-phenanthroline methiodide (0·5 g.) (Haworth and Sykes, *loc. cit.*) was oxidised in water (25 c.c.) with 10% sodium hydroxide solution (2 c.c.) and 10% potassium ferricyanide solution (10 c.c.). The dark tar, which separated from the turbid mixture on basificationafter 30 min., was heated in dilute hydrochloric acid solution for 30 min. at 100°. This solution was cooled and made strongly alkaline, and the brown precipitate was dried and extracted with a small volume of chlorobenzene, to yield a few mg. of crystalline material, m. p. 296° with previous darkening and softening. This, on admixture, did not depress the m. p. of the above amino-compound.

5-Amino-3 : 4-dihydro-4-methyl-3-oxo-4 : 7-phenanthroline (II; R = NH_2, R′ = H) was obtained by treatment of the chloro-base (II; R = Cl, R′ = H) (1 g.) as described above for the isomeric chloro-compound except that purification of the product by way of its hydrochloride was omitted. The *amino*-compound (0·2 g.), which was extracted by benzene from the crude product, crystallised from chlorobenzene (charcoal) in yellow prismatic needles, m. p. 257° with previous darkening and softening (Found: C, 69·2; H, 4·9; N, 18·8%).

4 : 7-Phenanthroline Methiodide (I; X = I, R = R′ = H).—**4 : 7**-Phenanthroline (5·4 g.), prepared by a double Skraup reaction on *NN′*-diacetyl-*p*-phenylenediamine in conditions similar to those of B.P. 394,416, ex. 11, was heated with excess of methanolic methyl iodide (20 c.c. of 40% w/v) in a sealed flask at 100° for 30 min. The solid product, after being washed with ether, was crystallised from water (75 c.c.), to yield as first crop 6—7 g. of the yellow monomethiodide monohydrate (Skraup and Vortmann, *Monatsh.*, 1883, **4**, 570; Kaufmann and Radošević, *loc. cit.*) which was recrystallised from water and dried at 100° to the orange anhydrous salt, m. p. 268° (decomp.) with previous darkening and softening (Douglas, Jacomb, and Kermack, *loc. cit.*, give m. p. 270—271°) (Found, for anhyd. material: I, 39·4. Calc. for $C_{13}H_{10}N_2ClI$: I, 39·4%). The original mother-liquor, after concentration, deposited a mixture of the monomethiodide and dichromate-orange prisms of the dimethiodide.

Pyr- *or* Pyr′-*Amino-3 : 4-dihydro-4-methyl-3-oxo-4 : 7-phenanthroline.*—The nitro-compound (5 g.), prepared (Kaufmann and Radošević, *loc. cit.*) by nitrating the nitrate of the oxidation product (Douglas, Jacomb, and Kermack, *loc. cit.*) of 4 : 7-phenanthroline methiodide, was boiled under reflux for 30 min. with yellow ammonium sulphide solution (40 c.c. of 12% w/v H_2S) and water (60 c.c.). The product was acidified with dilute sulphuric acid, boiled, and

filtered while hot. The filtrate, made alkaline with ammonia and cooled, deposited the crude amino-derivative (3·5 g.) which crystallised from chlorobenzene in yellow plates, m. p. 246° (Kaufmann and Radošević, *loc. cit.*, give m. p. 250°). Like the *Bz*-substituted isomers, this compound had a nitrate and a hydrochloride which were sparingly soluble in the respective dilute acids. Its m. p. was obviously distinct from that of the 5-amino-7 : 8-dihydro-compound and somewhat removed from that of the 5-amino-3 : 4-dihydro-compound; on admixture, it depressed the m. p. of the latter.

6-*Nitroquinoline.*—A mixture of the sodium salt of 2-amino-5-nitrobenzenesulphonic acid (180 g.), water (540 c.c.), concentrated sulphuric acid (540 c.c.), glycerol (270 c.c.), and arsenic acid (270 c.c.; *d* 1·8) was boiled under reflux for 3—4 hr. The product was cooled, diluted, and neutralised, yielding a precipitate (85 g.) which crystallised from dilute acetic acid or alcohol (charcoal) in colourless needles; the purified material was free from sulphur, and its m. p. 151° was not depressed on admixture with authentic 6-nitroquinoline prepared by a Skraup reaction on *p*-nitroaniline in the conditions of B.P. 394,416, ex. 8.

The quaternary salts described herein were dried at 100°, and none lost any significant further proportion of water at 100° *in vacuo* over phosphoric oxide.

My thanks are offered to Mr. P. S. Diamond for assistance in some of the preparative work.

Department of Biochemistry, Charing Cross Hospital Medical School,
13, William IV Street, London, W.C.2. [*Received, July 3rd,* 1953.]

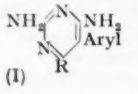
713. *Synthesis of* 2 : 6-*Diamino*-3-*arylpyridines.*

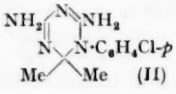
By B. H. Chase and James Walker.

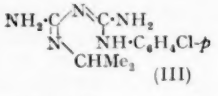
2 : 6-Diamino-3-phenylpyridine and 2 : 6-diamino-3-*p*-chlorophenylpyridine were required for examination for antimalarial activity in view of their relation to other highly active compounds. Methods for their synthesis *via* 3-aryl-2 : 6-dihydroxypyridines are described.

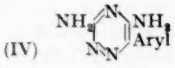
The outstanding antimalarial activity of 2 : 4-diamino-5-arylpyrimidines (I; R = H or alkyl) (Falco, Goodwin, Hitchings, Rollo, and Russell, *Brit. J. Pharmacol.*, 1951, **6**, 185; Chase, Thurston, and Walker, *J.*, 1951, 3439) and of 4 : 6-diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (II), the biologically active metabolite of proguanil (III) (Carrington, Crowther, Davey, Levi, and Rose, *Nature*, 1951, **168**, 1080), made desirable a further study of the relationship between structure and biological activity amongst appropriately substituted diamino-heterocyclic compounds. Antimalarial activity, for example, is retained in the *as*-triazine series (IV) (Hitchings, Maggiolo, Russell, VanderWerff, and Rollo, *J. Amer. Chem. Soc.*, 1952, **74**, 3201), but it is lost when the six-membered hetero-ring is replaced by a five-membered ring as in 3 : 5-diamino-1-aryl-1 : 2 : 4-triazoles (1-arylguanazoles) (V) (Thurston and Walker, *J.*, 1952, 4542). The work described in the present communication was carried out to see whether the antimalarial activity of (I) would be retained in 2 : 6-diamino-3-arylpyridines (VI), in which one of the ring-nitrogen atoms (N_1) of (I) is replaced by a =CH– group.

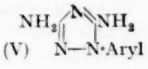
An attractive direct route to diaminopyridines of type (VI) would appear to be by Tschitschibabin amination (Tschitschibabin and Seide, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1216) of the appropriate 3-arylpyridines but the latter are unfortunately not readily accessible. We therefore turned to the synthesis, as intermediates, of 3-aryl-2 : 6-


(I)


(II)


(III)

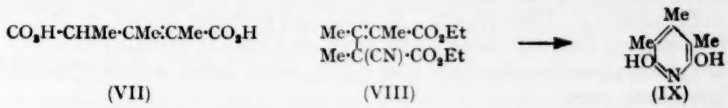

(IV)


(V)

(VI)

dihydroxypyridines, which are, of course, tautomeric forms of the imides of α-arylglutaconic acids, and it was expected that these would be convertible into 3-aryl-2 : 6-dichloropyrid-

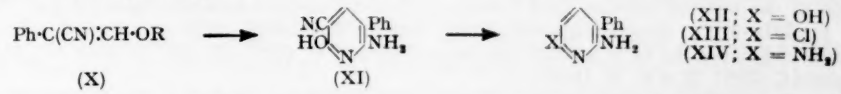
ines and thence into the required 2 : 6-diamino-3-arylpyridines (VI). Several alkyl-substituted 2 : 6-dihydroxypyridines have been prepared from alkylated glutaconic esters and ammonia (Ruhemann, *J.*, 1893, **63**, 259, 874; 1899, **75**, 249) but there are advantages to be gained in having the nitrogen atom of the pyridine ring provided by the cyano-group of alkylated cyanoglutaconic esters (Rogerson and Thorpe, *J.*, 1905, **87**, 1685) or by a carbamyl group (cf. Errera, *Ber.*, 1898, **31**, 1241). The tendency for the formation of the dihydroxypyridine in such cases is quite marked, since, for example, an attempt to prepare αβγ-trimethylglutaconic acid (VII) by hydrolysis of diethyl α-cyano-αβγ-trimethylglutacon-



(VII) (VIII) (IX)

ate (VIII) gave 2 : 6-dihydroxy-3 : 4 : 5-trimethylpyridine (IX) in 56% yield (Adams, VanDuuren, and Braun, *J. Amer. Chem. Soc.*, 1952, **74**, 5608; cf. Thorpe, *J.*, 1905, **87**, 1682). Overall yields in these syntheses of alkylated 2 : 6-dihydroxypyridines, however, are rarely good and few have approached that (85%) claimed by Ruzicka and Fornasir (*Helv. Chim. Acta*, 1919, **2**, 344) in their related synthesis of 3-cyano-5-ethyl-2 : 6-dihydroxy-4-methylpyridine.

No 3-aryl derivatives of 2 : 6-dihydroxypyridine appear to have been studied and it seemed more promising to attempt their synthesis directly from cyano- or carbamyl-substituted α-arylglutaconic esters, particularly since better yields of intermediates were to be expected from cyanoacetic acid derivatives than from malonic acid or ester (cf. Rogerson and Thorpe, *loc. cit.*; Ruzicka and Fornasir, *loc. cit.*), rather than to aim at the α-arylglutaconic esters with subsequent imide formation. The general method of Rogerson and Thorpe (*loc. cit.*) for the preparation of 3-alkyl-2 : 6-dihydroxy-4-methylpyridines, involving the condensation of ethyl sodiocyanoacetate with ethyl α-alkylacetoacetic esters, did not appear to us as attractive as a method based on Errera's condensation (*loc. cit.*) of ethyl ethoxymethylenecyanoacetate with ethyl sodiocyanoacetate, in view of our familiarity with alkoxymethylenearylacetonitriles (Chase, Thurston, and Walker, *loc. cit.*; Chase and Walker, *J.*, 1953, 3518), which also offered the possibility of introducing one amino-group directly. This was indeed realised, since methoxymethylene- or *iso*butoxymethylene-phenylacetonitrile (X) underwent smooth condensation with sodiocyanoacetamide to give 2-amino-5-cyano-6-hydroxy-3-phenylpyridine (XI) in good yield, and the 4-methyl derivative of (XI) was obtained from β-*iso*butoxy-α-phenylcrotononitrile. Prolonged treatment, however, was necessary to effect hydrolysis and decarboxylation of (XI) with the result that only moderate yields of 2-amino-6-hydroxy-3-phenylpyridine (XII) were obtained, and the related amide was also isolated when the time of hydrolysis was appreciably curtailed. Conversion of (XII) into 2-amino-6-chloro-3-phenylpyridine (XIII) with phosphoryl chloride required vigorous conditions and so did the conversion of (XIII) into the desired 2 : 6-diamino-3-phenylpyridine (XIV), the overall yield from the alkoxymethylenephenylacetonitrile being ~16%.

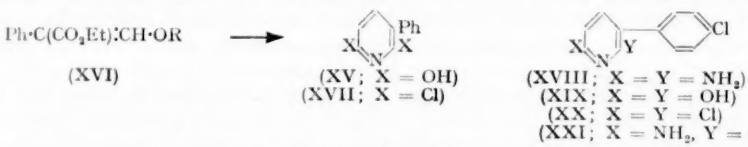


(X) (XI)

As an alternative, (XIV) was sought by way of 2 : 6-dihydroxy-3-phenylpyridine (XV) and this route called for alkoxymethylene derivatives (XVI) of phenylacetic ester. The alkylation of ethyl α-formylphenylacetate has been studied by Wislicenus and von Schrötter (*Annalen*, 1921, **424**, 215) who found *C*-alkylation to occur almost exclusively with methyl and ethyl iodide but *O*-alkylation to take place mainly with methyl and ethyl sulphate. As methylation of the related α-formylphenylacetonitrile with methyl iodide and potassium carbonate in acetone is a convenient method for the preparation of (X; R = Me) (Chase, Thurston, and Walker, *loc. cit.*), the same conditions were applied to ethyl α-formylphenylacetate and, in contrast with Wislicenus and von Schrötter's observations, the major

product was ethyl methoxymethylenephenylacetate (XVI; R = Me). The most convenient route to the *O*-alkyl derivatives (XVI) of ethyl α-formylphenylacetate, however, is by acid-catalysed etherification (cf. Chase and Walker, *loc. cit.*). Condensation of either ethyl methoxymethylenephenylacetate or ethyl *iso*butoxymethylenephenylacetate with sodiocyanoacetamide and hydrolysis of the intermediate product gave 2 : 6-dihydroxy-3-phenylpyridine (XV), which was also obtained by ammonolysis of dimethyl α-phenylglutaconate. Subsequent conversion of (XV) into 2 : 6-dichloro-3-phenylpyridine (XVII) with phosphoryl chloride also required vigorous conditions and the addition of phosphorus pentachloride introduced unwanted chlorine atoms, as is well known in the pyridine series (cf. Sell and Dootson, *J.*, 1898, **73**, 432; Ruzicka and Fornasir, *loc. cit.*, p. 346). Amination of (XVII) then gave 2 : 6-diamino-3-phenylpyridine (XIV) in overall yields of ~19% from ethyl alkoxymethylenephenylacetate and ~11% from ethyl α-formylphenylacetate *via* α-phenylglutaconic acid.

Since optimal biological activity would be expected in the *p*-chlorophenyl analogue, 2 : 6-diamino-3-*p*-chlorophenylpyridine (XVIII) was synthesised from ethyl α-*p*-chlorophenyl-α-formylacetate *via* 3-*p*-chlorophenyl-2 : 6-dihydroxypyridine (XIX) and 2 : 6 : 4′-trichloro-3-phenylpyridine (XX) by methods similar to those described above. Difficulty was experienced, however, in the amination of 2 : 6 : 4′-trichloro-3-phenylpyridine (XX) because of the risk of replacing only one or all three chlorine atoms by amino-groups. Only one amino-group was introduced with ethanolic ammonia at 210° in the presence of copper powder or with phenol and ammonium carbonate at 195°, the product being pre-



sumably 6-amino-2-chloro-3(or 5)-*p*-chlorophenylpyridine (XXI), while aqueous ethanolic ammonia at 180—185° in the presence of copper sulphate introduced either two or three amino-groups giving 2 : 6-diamino-3-*p*-chlorophenylpyridine (XVIII) or 2 : 6 : 4′-triamino-3-phenylpyridine.

We are indebted to Miss W. A. F. Webber for kindly carrying out biological tests on compounds (XII), (XIII), (XIV), (XVIII), and (XXI); they were quite toxic and none appeared to be active in tolerated doses against *P. berghei* in the mouse, or against *T. equiperdum*. The high antimalarial activity of (I) therefore is lost when the pyrimidine ring is replaced by a pyridine ring, and toxicity is increased.

Experimental

2-Amino-5-cyano-6-hydroxy-3-phenylpyridine (XI).—(*A*) Cyanoacetamide (8·4 g.) and methoxymethylenephenylacetonitrile (15·9 g.) (Chase, Thurston, and Walker, *loc. cit.*) were added in succession to sodium ethoxide (from 2·3 g. of sodium) in ethanol (100 c.c.). The mixture was boiled under reflux for 2 hr., diluted with water, and extracted with ether. Acidification of the aqueous solution gave *2-amino-5-cyano-6-hydroxy-3-phenylpyridine* (16·4 g., 78%), m. p. 307—310°. Recrystallisation from dimethylformamide–ethanol afforded colourless prisms and raised the m. p. to 320° (decomp.) (Found: C, 67·9; H, 4·2; N, 19·8. $C_{12}H_9ON_3$ requires C, 68·2; H, 4·3; N, 19·9%).

(*B*) A mixture of *iso*butoxymethylenephenylacetonitrile (100·6 g.) (Chase and Walker, *loc. cit.*), cyanoacetamide (42 g.), and sodium ethoxide (from 11·5 g. of sodium) in absolute ethanol (300 c.c.) was boiled under reflux in a slow stream of nitrogen for 6 hr., yielding 2-amino-5-cyano-6-hydroxy-3-phenylpyridine (85·8 g., 81%), m. p. 310°, identical with the preceding product.

Acetylation (of 1·0 g.) with acetic anhydride (5 c.c.) and pyridine (5 c.c.) at the b. p. afforded *2-acetamido-5-cyano-6-hydroxy-3-phenylpyridine*, which separated from methoxyethanol in pale yellow prisms (1·06 g.), m. p. 279—281° (Found: C, 66·6; H, 4·2; N, 16·4. $C_{14}H_{11}O_2N_3$ requires C, 66·4; H, 4·4; N, 16·6%).

2-Amino-6-chloro-5-cyano-3-p henylpyridine.—A mixture of 2-amino-5-cyano-6-hydroxy-3-

phenylpyridine (1·0 g.) and phosphoryl chloride (3 c.c.) was heated in a sealed tube at 150° for 3 hr. The black residue was poured on ice, maintained just alkaline with aqueous ammonia, and thoroughly extracted with benzene. Removal of the solvent and recrystallisation of the residue from ethyl acetate–light petroleum afforded *2-amino-6-chloro-5-cyano-3-phenylpyridine* in colourless plates (0·24 g.), m. p. 216—217° (Found : C, 62·9; H, 3·4; N, 18·3. $C_{12}H_8N_3Cl$ requires C, 62·8; H, 3·5; N, 18·3%).

2-Amino-6-hydroxy-3-phenylpyridine (XII).—2-Amino-5-cyano-6-hydroxy-3-phenylpyridine (5 g.) was hydrolysed with concentrated hydrobromic acid (50 c.c.) and glacial acetic acid (50 c.c.) for 21 hr. under reflux. Removal of the solvent under reduced pressure and trituration of the residue with water (50 c.c.) and chloroform (50 c.c.) gave an almost colourless solid (3·9 g.). On crystallisation from aqueous acetic acid, *2-amino-6-hydroxy-3-phenylpyridine* separated in colourless needles (1·96 g., 44%), m. p. 235—237° (Found : C, 71·0; H, 5·3; N, 15·2. $C_{11}H_{10}ON_2$ requires C, 71·0; H, 5·4; N, 15·0%). The crude material appeared to contain a considerable proportion of another substance which, however, was not isolated. When the hydrolysis was carried out for only 6 hr., *2-amino-6-hydroxy-3-phenylpyridine-5-carboxyamide* was also isolated; it separated from aqueous acetic acid in colourless prisms, m. p. 282—284° (Found : C, 62·7; H, 4·8; N, 18·5. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%). Both compounds acquired a pink to purple colour when kept in the dry state or in solution.

2-Amino-6-chloro-3-phenylpyridine (XIII).—A mixture of 2-amino-6-hydroxy-3-phenylpyridine (2·0 g.) and phosphoryl chloride (5 c.c.) was heated in a sealed tube at 170—175° for 4 hr. The cooled residue was poured on ice and kept alkaline by addition of aqueous ammonia. Extraction with benzene and removal of the solvent left a residue which crystallised from benzene–light petroleum in tan-coloured needles (1·23 g., 56%), m.p. 153—155°. Pure *2-amino-6-chloro-3-phenylpyridine*, sublimed at 150°/15 mm., separated from light petroleum in colourless plates, m. p. 155—157° (Found : C, 65·0; H, 4·3. $C_{11}H_9N_2Cl$ requires C, 64·6; H, 4·4%).

2-Amino-5-cyano-6-hydroxy-4-methyl-3-phenylpyridine.—A mixture of β-*iso*butoxy-α-phenylcrotononitrile (9·2 g.) (Chase and Walker, *loc. cit.*), cyanoacetamide (3·6 g.), and sodium ethoxide (from 1·0 g. of sodium) in absolute ethanol (100 c.c.) was boiled under reflux for 3 hr. The alkali-soluble fraction, isolated in the usual way, afforded *2-amino-5-cyano-6-hydroxy-4-methyl-3-phenylpyridine*, which separated from methoxyethanol in colourless needles (3·1 g.), m. p. 346° (decomp.) (Found : C, 69·6; H, 5·0; N, 18·6. $C_{13}H_{11}ON_3$ requires C, 69·3; H, 4·9; N, 18·7%).

Ethyl α-Formylphenylacetate.—Ethyl phenylacetate (142 g.) was formylated as described by Wislicenus (*Annalen*, **1896**, **291**, 164), and the colourless product (117 g.), b. p. 89—91°/0·03 mm., n_D^{19} 1·5386, partly solidified on standing. This material was used in the following experiments without separation of the *cis*- and *trans*-(enolic) forms.

Ethyl Methoxymethylenephenylacetate (XVI; R = Me).—A vigorously stirred mixture of ethyl α-formylphenylacetate (100 g.), methyl iodide (111 g.), and anhydrous potassium carbonate (72 g.) in dry acetone (500 c.c.) was boiled under reflux for 6 hr. Most of the acetone was then removed by distillation and the mixture, diluted with ether (500 c.c.), was filtered, the cake being washed with ether (350 c.c.). The combined ethereal solutions were washed with cold N-sodium hydroxide (250 c.c.) and with water (100 c.c.), then dried and evaporated. Fractionation of the residue gave (i) an oil (43 g.), b. p. 60—114°/0·8 mm., doubtless consisting largely of ethyl α-formyl-α-phenylpropionate, and (ii) ethyl methoxymethylenephenylacetate as a colourless oil (60·5 g.), b. p. 114—119°/0·8 mm., n_D^{19} 1·5480 (Found : C, 69·9; H, 6·8; OMe + OEt, 35·6. Calc. for $C_{12}H_{14}O_3$: C, 69·9; H, 6·8; OMe + OEt, 36·9%). Wislicenus and von Schrötter (*loc. cit.*) record b. p. 173—175°/15 mm., m. p. 54—55°, for this substance prepared by using methyl sulphate and aqueous sodium hydroxide.

Ethyl iso*Butoxymethylenephenylacetate* (XVI; R = Bu^i).—A mixture of ethyl α-formylphenylacetate (67 g.), *iso*butanol (37 g.), and toluene-*p*-sulphonic acid (5·9 g.) in benzene (250 c.c.) was boiled under reflux for 4 hr., a conventional Dean and Stark separator being used (cf. Chase and Walker, *loc. cit.*). The benzene solution was washed with cold 0·5N-sodium hydroxide solution (2 × 150 c.c.), and with water, and was then fractionated after addition of a drop of concentrated sulphuric acid, affording *ethyl* iso*butoxymethylenephenylacetate* as a colourless oil (74·8 g., 87%), b. p. 134—138°/2 mm., 126°/0·6 mm., n_D^{19} 1·5251 (Found : C, 72·6; H, 8·1. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%).

2 : 6-Dihydroxy-3-phenylpyridine (XV).—(*A*) Cyanoacetamide (18·6 g.) and ethyl methoxymethylenephenylacetate (43·5 g.) were added in succession to a solution of sodium ethoxide (from 5·1 g. of sodium) in absolute ethanol (total volume, 175 c.c.). After 4½ hr. at the b. p. under reflux, the mixture was kept at room temperature for 36 hr., then diluted with water (*ca.* 1 l.) and extracted with ether. The aqueous solution was acidified with 10N-hydrochloric acid and

cooled to 5°. The pale buff precipitate was collected and dried (yield, 30·1 g.). This material (21 g.) was boiled under reflux for 19 hr. with acetic acid (25 c.c.) and hydrobromic acid (150 c.c.; *d* 1·48). After removal of the solvent under reduced pressure, water (75 c.c.) was added, and the insoluble material was filtered off and washed with water and with ether. The resulting 2 : 6-*dihydroxy*-3-*phenylpyridine* separated from aqueous acetic acid, or from *iso*propanol, in needles (11·2 g.), m. p. 214° (deep red melt), which became pink in air (Found : C, 70·3; H, 5·0; N, 7·7. $C_{11}H_9O_2N$ requires C, 70·6; H, 4·9; N, 7·5%). Similar results were obtained on use of ethyl methoxymethylenephenylacetate prepared (without purification) by the action of diazomethane on ethyl α-formylphenylacetate.

(*B*) The use of ethyl *iso*butoxymethylenephenylacetate in the above condensation, hydrolysis of the crude intermediate, and crystallisation from *iso*propanol gave 2 : 6-dihydroxy-3-phenylpyridine (31% yield), identical with the above material.

α-Phenylglutaconic Acid.—Ethyl α-formylphenylacetate (38 g.) was treated with malonic acid (22 g.) in pyridine (20 g.) as described by Borsche and Niemann (*Ber.*, 1936, **69**, 1993). The crude product (34 g.) was triturated with carbon tetrachloride to yield α-phenylglutaconic acid (20·5 g., 48%) as a cream-coloured solid, m. p. 153—158°. Addition of piperidine (1 g.) to the reaction mixture raised the yield to 60%. Recrystallisation from water gave clusters of colourless needles, m. p. 165—167°; Borsche and Niemann (*loc. cit.*) record m. p. 166—167°. The acid (10 g.) was refluxed for 5 hr. with 5% methanolic sulphuric acid (100 c.c.), affording the dimethyl ester as a colourless oil (9·9 g., 87%), b. p. 121—122°/0·2 mm., n_D^{22} 1·5309; Borsche and Niemann (*loc. cit.*) record b. p. 180—182°/15 mm.

Pyrolysis of Ammonium α-Phenylglutaconate.—A solution of α-phenylglutaconic acid (2·06 g.) in excess of concentrated aqueous ammonia was evaporated under reduced pressure and the residue was twice taken to dryness with ethanol. The resulting ammonium salt was heated to 180—190° (oil-bath) under reduced pressure in a flask fitted with a short air-condenser. When evolution of gas had ceased (after 15 min.) the residue was taken up in 5% aqueous sodium carbonate, and the solution was extracted with ether. The aqueous phase was acidified with hydrochloric acid and again extracted with ether. Removal of the ether from the latter (dried) extract gave 4-phenylbut-3-enoic acid (phenyl*iso*crotonic acid), which separated from light petroleum and from aqueous methanol in colourless needles (1·56 g.), m. p. 85—86° (Found : C, 73·7; H, 6·0. Calc. for $C_{10}H_{10}O_2$: C, 74·0; H, 6·2%). Buchner and Dessauer (*Ber.*, 1892, **25**, 1155) record m. p. 88°.

The product was further characterised as the amide : the methyl ester (prepared by using diazomethane) was set aside at 37° for 48 hr. with concentrated aqueous ammonia, and the resulting amide separated from aqueous ethanol in colourless prisms, m. p. 130—131°. Köhl (*Ber.*, 1903, **36**, 174) records m. p. 130°.

Ammonolysis of Dimethyl α-Phenylglutaconate.—Dimethyl α-phenylglutaconate (4·68 g.) and ethanolic ammonia solution (60 c.c., saturated at 0°) were heated in a glass-lined steel bomb-tube at 130° for 4 hr. The solution was cooled to 5° overnight and the resulting 2 : 6-dihydroxy-3-phenylpyridine (1·60 g., 43%; m. p. 208—209°) was collected. Recrystallisation from *iso*propanol gave colourless needles, m. p. 213—214°, identical with the product obtained by the alternative method described above.

2 : 6-*Dichloro*-3-*phenylpyridine* (XVII).—A mixture of 2 : 6-dihydroxy-3-phenylpyridine (4·0 g.) and phosphoryl chloride (8·0 c.c.) was heated in a sealed tube at 200—210° for 4½ hr. The cooled residue was poured on ice with addition of aqueous ammonia to maintain neutrality. The product was recovered by extraction with chloroform and sublimed at 0·5 mm. (bath 90—130°), affording a white crystalline solid (4·15 g., 87%), m. p. 91·5—93·5°. 2 : 6-*Dichloro*-3-*phenylpyridine* separated from light petroleum in large prisms, m. p. 95—96° (Found : C, 59·2; H, 2·9; N, 6·0; Cl, 31·3. $C_{11}H_7NCl_2$ requires C, 59·0; H, 3·2; N, 6·3; Cl, 31·6%).

The dichloro-compound (500 mg.) in ethanol (75 c.c.) containing N-sodium hydroxide (5·6 c.c.) was shaken with 2% palladised strontium carbonate (500 mg.) in hydrogen at room temperature and atmospheric pressure. Uptake of hydrogen was complete in 2 hr. and the mixture was filtered and concentrated under reduced pressure. The product, recovered in ether and washed with water, was isolated and treated with alcoholic picric acid, yielding 3-phenylpyridine picrate (800 mg., 93%), m. p. 159—160°, not depressed on admixture with the specimen obtained from the tetrachloropyridine (below).

2 : 4 : 5 : 6-*Tetrachloro*-3-*phenylpyridine.*—A mixture of 2 : 6-dihydroxy-3-phenylpyridine (1·87 g.), phosphoryl chloride (5 c.c.) and phosphorus pentachloride (5·1 g.) was boiled gently under reflux for 2 hr. The phosphoryl chloride was largely removed under reduced pressure and the residue was treated with ice and dilute aqueous ammonia. Extraction with benzene and

evaporation of the solvent gave a residue (0·86 g.), which, after passage in benzene through a column of alumina, yielded 2 : 4 : 5 : 6-*tetrachloro*-3-*phenylpyridine* (0·33 g.), separating from light petroleum in colourless needles, m. p. 101—103° (Found: C, 45·3; H, 1·8; N, 5·2; Cl, 48·7. $C_{11}H_5NCl_4$ requires C, 45·1; H, 1·7; N, 4·8; Cl, 48·4%).

The substance (250 mg.) was dechlorinated in the manner described above for 2 : 6-dichloro-3-phenylpyridine, absorption of hydrogen ceasing in 12 hr. 3-Phenylpyridine picrate separated from alcohol in yellow needles (260 mg., 79%), m. p. 159—160°, not depressed on admixture with the previous specimen (Found: C, 53·3; H, 3·1; N, 14·1. Calc. for $C_{11}H_9N,C_6H_3O_7N_3$: C, 53·1; H, 3·1; N, 14·6%). Hey and Walker (*J.*, 1948, 2218) record m. p. 163°.

No pure products could be isolated after 2 : 6-dihydroxy-3-phenylpyridine had been refluxed with phosphoryl chloride (with or without the addition of dimethylaniline), or with thionyl chloride.

2 : 6-*Diamino*-3-*phenylpyridine* (XIV).—(*A*) A mixture of 2-amino-6-chloro-3-phenylpyridine (1·0 g.), aqueous ammonia (20 c.c.; *d* 0·880), ethanol (10 c.c.), and copper sulphate pentahydrate (1 g.) was heated in a glass-lined steel bomb-tube at 180° for 3 hr. The mixture was diluted with water (25 c.c.) and thoroughly extracted with ether. The residue (850 mg.) left on removal of the ether was chromatographed on alumina and elution with chloroform afforded 2 : 6-*diamino*-3-*phenylpyridine* (680 mg., 75%) (Found: C, 71·1; H, 6·2. $C_{11}H_{11}N_3$ requires C, 71·3; H, 6·0%). This specimen crystallised from light petroleum in plates, m. p. 90°, with re-solidification and subsequent melting at 114—115°. After sublimation at 15 mm. only the higher-melting form was obtained, m. p. 114—115°, not depressed on admixture with 2 : 6-diamino-3-phenylpyridine prepared from 2 : 6-dichloro-3-phenylpyridine (below).

(*B*) A mixture of 2 : 6-dichloro-3-phenylpyridine (500 mg.), aqueous ammonia (20 c.c.; *d* 0·880), ethanol (10 c.c.), and copper sulphate pentahydrate (500 mg.) was heated in a glass-lined steel bomb tube at 200° for 6 hr. The cooled solution was thoroughly extracted with ether, and the extract was washed with water, dried, and evaporated. The green residue (400 mg.) was chromatographed on alumina (15 × 1·5 cm.) and elution with chloroform–methanol (9 : 1) afforded 2 : 6-diamino-3-phenylpyridine, separating from light petroleum in colourless plates (290 mg., 70%), m. p. 112—113° (Found: C, 71·6; H, 5·9; N, 22·7. Calc. for $C_{11}H_{11}N_3$: C, 71·3; H, 6·0; N, 22·7%).

Ethyl α-p-*Chlorophenyl*-α-*formylacetate*.—A mixture of ethyl *p*-chlorophenylacetate (90 g.) and ethyl formate (62 c.c.) was added to sodium wire (11·5 g.) in dry ether (450 c.c.) cooled to 5°. The temperature was kept at ~5° during the ensuing vigorous reaction (2—3 hr.) and the mixture was then kept at room temperature overnight. Ice-water was added and the aqueous layer was extracted with ether, acidified with dilute sulphuric acid, and again thoroughly extracted with ether. The ether was removed and the residue (92 g., 83%), dried by azeotropic distillation with benzene, readily solidified. *Ethyl* α-p-*chlorophenyl*-α-*formylacetate* (68 g., 60%) distilled at 120—125°/0·1 mm. and recrystallised from light petroleum, gave colourless needles, m. p. 45—46° (Found: C, 58·0; H, 4·8. $C_{11}H_{11}O_3Cl$ requires C, 58·3; H, 4·9%). Distillation was attended by considerable loss and the substance was used without distillation in the following reactions.

Ethyl α-p-*Chlorophenyl*-α-*ethoxymethyleneacetate*.—A mixture of ethyl α-*p*-chlorophenyl-α-formylacetate (100 g.), ethanol (46 g.) and toluene-*p*-sulphonic acid (5 g.) in benzene (200 c.c.) was boiled under reflux, using the Dean and Stark separator, until no more water was evolved (9 hr.). The benzene solution was washed with cold 0·5N-potassium hydroxide, and with water. Fractionation then afforded: (i) fore-running (12 g.), b. p. 132—142°/1·2 mm., and (ii) *ethyl* α-p-*chlorophenyl*-α-*ethoxymethyleneacetate*, a colourless oil (82 g., 73%), b. p. 142—144°/1·2 mm., 128°/0·2 mm., $n_D^{19\cdot5}$ 1·5488 (Found: C, 61·0; H, 5·7. $C_{13}H_{15}O_3Cl$ requires C, 61·3; H, 5·9%).

Ethyl iso*Butoxymethylene*-p-*chlorophenylacetate*.—In a similar manner, ethyl *p*-chlorophenylformylacetate (10 g.), *iso*butanol (4·0 g.), and toluene-*p*-sulphonic acid (1 g.) in benzene (100 c.c.) afforded *ethyl* iso*butoxymethylene*-p-*chlorophenylacetate* as a colourless oil (10·3 g., 83%), b. p. 137—141°/0·15 mm., n_D^{20} 1·5362 (Found: C, 63·9; H, 6·6; Cl, 12·3. $C_{15}H_{19}O_3Cl$ requires C, 63·7; H, 6·8; Cl, 12·5%).

α-p-*Chlorophenylglutaconic Acid*.—Ethyl *p*-chlorophenylformylacetate (100 g.), malonic acid (49 g.), pyridine (50 c.c.), and piperidine (1 g.) were heated together on the steam-bath for 5 hr. The resulting α-*p*-chlorophenylglutaconic acid (46·3 g., 44%; m. p. 175—179°), isolated as for α-phenylglutaconic acid, was well washed with carbon tetrachloride, and recrystallisation from ethyl acetate–light petroleum afforded colourless needles, m. p. 183—185° (Found: C, 54·6; H, 3·9. Calc. for $C_{11}H_9O_4Cl$: C, 54·9; H, 3·8%). Menon (*J.*, 1936, 1775) records m. p.

175° for this acid prepared in low yield from ethyl *p*-chlorophenylacetate and diethyl ethoxymethylenemalonate. The *diethyl* ester, prepared by azeotropic distillation in benzene with ethanol and toluene-*p*-sulphonic acid, was a colourless oil, b. p. 149°/0·4 mm., n_D^{22} 1·5275 (Found : C, 61·0; H, 5·8; Cl, 12·3. $C_{15}H_{17}O_4Cl$ requires C, 60·7; H, 5·8; Cl, 11·9%). In one experiment partial decarboxylation took place, yielding approximately equal amounts of the diethyl ester and *ethyl* 4-p-*chlorophenylbut*-3-*enoate*, b.p. 113°/0·15 mm., n_D^{22} 1·5500 (Found : C, 63·8; H, 5·8; Cl, 15·6. $C_{12}H_{13}O_2Cl$ requires C, 64·1; H, 5·8; Cl, 15·8%). Alkaline hydrolysis of the latter ester gave the free acid, which separated from light petroleum in irregular plates, m. p. 109—110° (Found : C, 61·1; H, 4·9; Cl, 17·8. Calc. for $C_{10}H_9O_2Cl$: C, 61·1; H, 4·6; Cl, 18·0%); Erdmann and Schwechten (*Annalen*, 1890, **260**, 65) record m. p. 108—109°.

3-p-*Chlorophenyl*-2 : 6-*dihydroxypyridine* (XIX).—(*A*) A solution of diethyl α-*p*-chlorophenylglutaconate (5·8 g.) in ethanolic ammonia (50 c.c.; saturated at 0°) was heated in a glass-lined steel bomb-tube at 150° for 5 hr. The resulting 3-p-*chlorophenyl*-2 : 6-*dihydroxypyridine* (1·07 g.) was collected and combined with a second crop (0·82 g.; total yield, 44%) obtained on concentration of the alcoholic solution. Recrystallisation from *iso*propanol gave woolly needles, m. p. 216—217° (Found : C, 59·8; H, 3·8; N, 6·0; Cl, 16·0. $C_{11}H_8O_2NCl$ requires C, 59·6; H, 3·6; N, 6·3; Cl, 16·0%).

(*B*) Ethyl *p*-chlorophenylethoxymethyleneacetate (31·8 g.) and cyanoacetamide (10·5 g.) were added to a solution of sodium ethoxide (from 3·0 g. of sodium) in absolute ethanol (100 c.c.); a thick cream-coloured sludge soon separated. More ethanol (100 c.c.) was added and the mixture was boiled under reflux for 8 hr., then poured into water, and the product was collected after acidification with 10N-hydrochloric acid. The moist paste was dehydrated by being suspended in glacial acetic acid (150 c.c.), the mixture being distilled until the b. p. reached 116°, with acetic acid added as required. Concentrated aqueous hydrobromic acid (150 c.c.) was then added and the mixture was boiled under reflux for 48 hr. The solvent was removed under reduced pressure and the residue, triturated with ether (200 c.c.) and water (100 c.c.) and cooled to 5°, was filtered off. Recrystallisation from *iso*propanol afforded woolly needles (5·8 g.) of the required chlorophenyldihydroxypyridine, m. p. 216—217°, alone and in admixture with the previous specimen (above). The mother-liquors and the ethereal washings yielded a further amount (3·3 g.; total yield, 33%) of the same substance, m. p. 214—216°. Similar yields of 3-*p*-chlorophenyl-2 : 6-dihydroxypyridine resulted from the use of the *iso*butyl enol ether.

In one experiment the precaution of dehydrating the pasty intermediate was not observed and hydrolysis was carried out for 18 hr. The product then isolated was 3-p-*chlorophenyl*-2 : 6-*dihydroxypyridine*-5-*carboxyamide*, which crystallised from dimethylformamide–ethanol in pale pink prisms, m. p. 280° (decomp.) (Found : C, 54·4; H, 3·6; N, 10·5. $C_{12}H_9O_3N_2Cl$ requires C, 54·5; H, 3·4; N, 10·6%).

2 : 6 : 4′-*Trichloro*-3-*phenylpyridine* (XX).—The foregoing *p*-chlorophenyldihydroxypyridine (4·0 g.) was heated with phosphoryl chloride (6 c.c.) in a sealed tube at 180° for 4 hr. The cooled residue was poured on ice, made alkaline with aqueous ammonia, and extracted with benzene. The dried solution was passed through a short column of alumina and evaporation then gave 2 : 6 : 4′-*trichloro*-3-*phenylpyridine* as a colourless crystalline mass (4·2 g., 90%), m. p. 135—136°; recrystallisation from light petroleum afforded colourless needles, m. p. 137—138° (Found : C, 51·2; H, 2·2; N, 5·4; Cl, 41·9. $C_{11}H_6NCl_3$ requires C, 51·1; H, 2·3; N, 5·4; Cl, 41·2%).

Ammonolysis of 2 : 6 : 4′-*Trichloro*-3-*phenylpyridine*.—(*A*) 2 : 6 : 4′-Trichloro-3-phenylpyridine (1·2 g.), copper powder (1 g.), and ethanolic ammonia (20 c.c., saturated at 0°) were heated in a glass-lined steel bomb-tube at 210° for 7 hr. After removal of the solvent under reduced pressure the residue was distributed between N-sodium hydroxide (50 c.c.) and chloroform (200 c.c.) and filtered, the chloroform layer then being separated and taken to dryness. The residue was chromatographed on alumina, and elution with benzene gave starting material (0·20 g., 17%), while elution with chloroform yielded a tan-coloured solid (0·90 g.), which proved to be 6-*amino*-2-*chloro*-3(or 5)-p-*chlorophenylpyridine* (XXI), separating from benzene in colourless needles (0·42 g., 45%), m. p. 186—187° (Found : C, 55·2; H, 3·3; N, 12·2. $C_{11}H_8N_2Cl_2$ requires C, 55·3; H, 3·4; N, 11·7%).

(*B*) 2 : 6 : 4′-Trichloro-3-phenylpyridine (1·5 g.), copper sulphate pentahydrate (1·5 g.), concentrated aqueous ammonia (30 c.c.), and ethanol (15 c.c.) were heated together in the glass-lined bomb-tube at 180—185° for 6 hr., the product being worked up as above and chromatographed on alumina. Elution with chloroform gave a tan-coloured solid (240 mg.), separating from benzene in colourless needles (130 mg., 15%), m. p. 185—186°, alone and in admixture with the monoamino-compound obtained above. Further elution with chloroform and with chloroform–methanol (20 : 1), followed by recrystallisation from benzene, afforded 2 : 6-*diamino*-

3-p-*chlorophenylpyridine* in the form of colourless needles (0·26 g., 20%), m. p. 114—115° (Found: C, 60·3; H, 4·5; N, 19·3. $C_{11}H_{10}N_3Cl$ requires C, 60·1; H, 4·6; N, 19·1%).

In another experiment, elution with chloroform–methanol (20 : 1) followed by recrystallisation from benzene yielded tan-coloured prisms (23%), m. p. 148—152°. Sublimation at 0·05 mm., followed by recrystallisation from benzene, gave colourless rhombs of 2 : 6 : 4′-*triamino*-3-*phenylpyridine*, m. p. 155—157° (Found: C, 66·4; H, 5·8; N, 28·3. $C_{11}H_{12}N_4$ requires C, 66·0; H, 6·0; N, 28·0%). 2 : 6-Diamino-3-*p*-chlorophenylpyridine (15%) was obtained from the mother-liquors.

(*C*) 2 : 6 : 4′-Trichloro-3-phenylpyridine (1·0 g.), phenol (5 g.), and ammonium carbonate (5 g.) were heated together in the bomb tube at 195° for 8 hr. The cooled residue was distributed between ether (500 c.c.) and 2N-sodium hydroxide solution (100 c.c.), and the residue left on evaporation of the ether was chromatographed on alumina. Elution with benzene gave colourless crystals (0·84 g.), m. p. 120—130°, which separated from light petroleum in long needles (0·49 g., 49%), m. p. and mixed m. p. with starting material, 137—138°. Elution with chloroform gave a tan-coloured solid (0·15 g.), separating from benzene in needles (70 mg., 8%), m. p. 185—186°, alone and in admixture with the monoamino-compound described above.

The authors are indebted to Mr. R. J. Clark and Mr. W. A. L. Marshment for preparative assistance.

National Institute for Medical Research,
The Ridgeway, Mill Hill, London, N.W.7. [*Received, July 18th*, 1953.]

---

714. *The Kinetics and Mechanisms of Nucleophilic Displacements in Allylic Systems. Part IV.* The Reaction of* 1 : 1-*Dimethylallyl Chloride with the Thiophenoxide Ion.*

By P. B. D. de la Mare and C. A. Vernon.

1 : 1-Dimethylallyl chloride reacts with sodium thiophenoxide by a reaction of the second order, to give the product, 3-methylbut-2-enyl phenyl sulphide, of substitution with anionotropic rearrangement. The reaction proceeds more rapidly, and has a lower energy of activation, than the corresponding reaction of 3 : 3-dichloroprop-1-ene. 1-Methylallyl chloride reacts, more slowly, but also by a reaction of the second order, to give a product from which can be isolated (cf. Cope, Morrison, and Field, *J. Amer. Chem. Soc.*, 1950, **72**, 59) the non-rearranged, contaminated with a small amount of the rearranged, product. The theoretical implications of these results are discussed.

In previous papers (Parts I—III, *J.*, 1952, 3326, 3331, 3628) it has been shown that bimolecular nucleophilic substitution with anionotropic rearrangement (S_N2') can be realised experimentally in allylic halides in which direct nucleophilic displacement (S_N2) is hindered by the presence of appropriate substituents at the reacting centre. A typical example is 3 : 3-dichloroprop-1-ene, in which the S_N2 reaction is hindered, and the S_N2' process is favoured, by the presence of the second chlorine substituent.

In 1 : 1-dimethylallyl chloride, $CH_2{:}CH{\cdot}CMe_2Cl$, the inductive effect of the two methyl substituents would be expected to inhibit somewhat the attack by a nucleophilic reagent at the double bond, but at the same time to facilitate the concerted removal of the chloride ion. Hence it could not be predicted *a priori* whether the S_N2' reaction would be faster for this than for simpler compounds.

The more usual reactions of 1 : 1-dimethylallyl chloride are unimolecular in character, as indicated by the fact that this compound and its allylic isomer, 3 : 3-dimethylallyl chloride (3-methylbut-2-enyl chloride), give on solvolysis similar mixtures of isomeric alcohols (Ultee, *Rec. Trav. chim.*, 1949, **68**, 483). It is also known (Young, Winstein, and Goering, *J. Amer. Chem. Soc.*, 1951, **73**, 1958) that solvolysis in acetic acid is accompanied by a rearrangement in which the ionisation of the migrating chlorine does not become complete, as is indicated by the non-intervention in the reaction of chloride ions from the environment.

* Part III, *J.*, 1952, 3628.

Sodium thiophenoxide, however, is a very powerful reagent for nucleophilic substitutions. Consistently, it has been found that 1 : 1-dimethylallyl chloride reacts with sodium thiophenoxide in alcohol by a reaction which is of the second order, is considerably faster than the corresponding solvolysis, and gives 3-methylbut-2-enyl phenyl sulphide.

This reaction does not involve a bimolecular displacement to form $CH_2{:}CH{\cdot}CMe_2{\cdot}SPh$, followed by rearrangement of the latter compound, for the following reason. Such a bimolecular displacement would of necessity be considerably slower than the corresponding bimolecular displacement of thiophenoxide ions on 1-methylallyl chloride, for it is well known that a retardation in rate results from the introduction of methyl substituents on a carbon atom undergoing bimolecular substitution, both for steric, and, as Dostrovsky, Hughes, and Ingold (*J.*, **1946**, 173) consider, for polar reasons. In the present instance, however, the introduction of the second methyl group has the result of facilitating, by a factor of about two, the observed rate of bimolecular displacement. Hence the more rapid reaction cannot be an S_N2 process. The possibility has also been excluded that the reaction involves an elimination to give isoprene, followed by the addition of thiophenol; for it has been shown that thiophenol does not add to isoprene under the conditions of the kinetic measurements. Taking into account these facts, together with the kinetic behaviour, the reaction can best be interpreted as a bimolecular substitution with anionotropic rearrangement (S_N2'). It proceeds some forty times more rapidly than the corresponding reaction of 3 : 3-dichloroprop-1-ene, and has a smaller energy of activation.

The reaction of 1-methylallyl chloride with sodium thiophenoxide in ethanol has been studied by Cope, Morrison, and Field (*J. Amer. Chem. Soc.*, 1950, **72**, 59). These workers isolated both 1-methylallyl and but-2-enyl phenyl sulphides from the product, the yields of pure isomers isolated being respectively 57 and 8%. Their work has been repeated, with essentially similar results. As judged from the refractive index of the product obtained by reaction at 5°, it contains only about 16% of the rearranged isomer, and this amount is somewhat increased when the temperature of the reaction is changed to 80°. Pure 1-methylallyl phenyl sulphide, after contact with sodium thiophenoxide, on recovery has increased refractive index, suggesting either that isomerisation occurs to the isomeric product under these conditions, or that the samples become contaminated with a trace of material of higher refractive index. The former possibility is the more likely, since in our experience fractionation or even simple distillation under reduced pressure of mixtures, which from their refractive index contain much 1-methylallyl phenyl sulphide, gives a distilled product containing an increased amount of the isomeric sulphide; no fractions of boiling points and refractive indices lower than those of 1-methylallyl phenyl sulphide, or higher than those of but-2-enyl phenyl sulphide, are obtained in these distillations.

It is considered, therefore, that the amount of but-2-enyl phenyl sulphide formed from 1-methylallyl chloride and sodium thiophenoxide by the S_N2' reaction, certainly less than 16% for reaction at 5°, is small, and probably approximates to the amount of rearranged ether formed in the reaction of this chloride with sodium ethoxide. For the latter reaction, Roberts, Young, and Winstein (*ibid.*, 1942, **64**, 2157) found less than 4% for reaction at 25°, and we have obtained only about 4·5% for reaction at 81° (cf. Catchpole and Hughes, *J.*, 1948, 4).

The following structural comparisons can now be made, using the data of earlier parts (*locc. cit.*):

Compound	$Me_2C(Cl){\cdot}CH{:}CH_2$	$Me{\cdot}CH(Cl){\cdot}CH{:}CH_2$	$Cl{\cdot}CH(Cl){\cdot}CH{:}CH_2$
k_2 (S_N2', for reaction with SPh^- in EtOH at 25°)...	0·090	>0·007	0·0025
E (kcal./mole)	19·6	—	21·2

It is clear that, so far as the effect of the methyl group on the S_N2' process is concerned, the facilitation of the breaking of the C–Cl bond dominates over the inductive retardation of attack by the nucleophilic reagent. In the S_N2' reaction, as in the S_N2 process (cf. Hughes, *Trans. Faraday Soc.*, 1941, **37**, 628), the polar requirements for the breaking of one bond are opposite to those required for the making of another, and hence the reaction may, in some circumstances, be facilitated either by electron-withdrawing or by electron-donating substituents. For the S_N2' process, it has now been made probable that

reactivity is enhanced both by a 1-chlorine (Part III, *loc. cit.*) and by a 1-methyl substituent, by facilitating, in the former case, the formation of the bond with the reagent, and in the latter, the breaking of the C–Cl bond. The effects of 2- and 3-substituents are under investigation; in these cases, it seems likely that the inductive influence on the formation of the new bond will become relatively of greater importance.

It is now becoming clear that S_N2' attack on the system $CH_2{:}C{\cdot}C{\cdot}Cl$ is more common than was once thought, and various examples have been recorded in the past without recognition of their mechanism. Thus, for example, we were unaware, when Part II was published, that 3 : 3-dichloroprop-1-ene has been recorded (Rothstein, *J.*, 1940, 1550) as reacting with the ethyl sulphide ion to give, in roughly equal amounts, 3 : 3-di(ethylthio)prop-1-ene and 1-chloro-3-ethylthioprop-1-ene. This reaction is probably bimolecular, and is analogous to the corresponding reaction of the thiophenoxide ion, in that products of normal and abnormal substitution are formed in nearly equal amounts. The differences in free energy of activation which determine the ratio of products for the reaction of 3 : 3-dichloroprop-1-ene with the different reagents OEt^-, SEt^-, OPh^-, SPh^- (cf. Part II, *loc. cit.*) are clearly rather small, and the presence of a second centre in the molecule, which may help attack on the unsaturated carbon atom by participation in a cyclic transition complex, is clearly advantageous for the observation of rearrangement, as Young, Webb, and Goering (*J. Amer. Chem. Soc.*, 1951, **73**, 1076) have demonstrated for the reaction of secondary amines with 1-methylallyl chloride.

Experimental

The general methods have been described in previous Parts (*locc. cit.*). 1 : 1-Dimethylallyl chloride, prepared as described by Ultee (*J.*, 1948, 530) and fractionated under reduced pressure, had b. p. 30°/120 mm. Its refractive index (n_D^{25} 1·4170) was always checked before use, to guard against isomerisation. 3 : 3-Dimethylallyl (3-methylbut-2-enyl) chloride, prepared similarly, had b. p. 112—115°/770 mm., n_D^{25} 1·4468.

3-*Methylbut-2-enyl phenyl sulphide* was prepared by the action of sodium thiophenoxide on 3-methylbut-2-enyl chloride in ethanol. The product had b. p. 124—126°/14 mm., f. p. −3·5°, n_D^{25} 1·5644 (Found: C, 74·2; H, 8·1. $C_{11}H_{14}S$ requires C, 74·2; H, 7·9%). Its sulphilimine derivative, prepared by the method of McCall, Tarbell, and Havill (*J. Amer. Chem. Soc.*, 1951, **73**, 4476), had m. p. 47° after recrystallisation from ethanol and from pentane.

1 : 1-Dimethylallyl chloride (20 g.) was allowed to react overnight at 30° with 250 ml. of N-sodium thiophenoxide in ethanol. The product was dissolved in ether, washed well with aqueous alkali and with water, and distilled, giving a sulphide (21 g.), b. p. 128—132°/16 mm., n_D^{25} 1·5632, f. p. −5·0°, not depressed on admixture with an authentic specimen. This material, and an authentic sample, were examined by Dr. L. C. Bateman and Dr. E. S. Waight, of the British Rubber Producers' Research Association, Welwyn Garden City, Herts. We are indebted to these investigators for showing that these two specimens had virtually identical infra-red spectra; the presence of bands at 1665 and 834 cm.$^{-1}$, together with the absence of bands at 1640 and 920 cm.$^{-1}$, were consistent with the structure $Me_2C{:}CH{\cdot}CH_2{\cdot}SPh$, and indicated contamination with less than 2% of $PhS{\cdot}CMe_2{\cdot}CH{:}CH_2$.

For the kinetic measurements, thiophenol was added to the equivalent amount of a standardised solution of sodium ethoxide in ethanol. This solution (*ca.* 100 ml.) was allowed to reach the temperature of the thermostat, and to it was added *ca.* 0·5 ml. of 1 : 1-dimethylallyl chloride. The following are details of a typical set of measurements, at 24·9°, in which 5·00-ml. portions were added to cooled alcohol containing 10 ml. of 0·0878N-hydrochloric acid, and back-titrated with 0·0190N-sodium hydroxide (lacmoid indicator); values of k_2 were calculated by using the usual formula $k_2 = 2{\cdot}303\{\log_{10}[b(a-x)/a(b-x)]\}/t(a-b)$, where b and a are the initial concentrations of the reactants, and x is the concentration of product at time t; E and B are the Arrhenius parameters, obtained from the equation $k_2 = Be^{-E/RT}$, the units of k_2 and B being l. mole^{-1} min.$^{-1}$, and E being in kcal./mole:

Time (min.)	0	7·30	16·75	26·70	34·6	48·0	83·0	∞
Titre (ml. 0·0190N-NaOH) ...	2·50	3·88	5·40	6·62	7·58	8·92	11·25	15·80
k_2 (l. mole^{-1} min.$^{-1}$)	—	0·092	0·092	0·088	0·089	0·090	0·089	—

From these values and those at other temperatures (35·1°, $k_2 = 0{\cdot}267$; 44·6°, $k_2 = 0{\cdot}701$) it can be deduced that the reaction has $E = 19{\cdot}6$ kcal., $\log_{10} B = 13{\cdot}35$. The reaction is bimolecular; the velocity coefficient at 44·6° ($k_2 = 0{\cdot}701$, for NaSPh = 0·159) is changed only

slightly, and in accordance with the usual small negative salt effect, by an increase in the concentration of sodium thiophenoxide ($k_2 = 0{\cdot}661$, for NaSPh = 0·220). The solvolysis of the halide is considerably slower. The following are details of the development of acid from 1 : 1-dimethylallyl chloride in ethanol at 44·6°; 5·53-ml. portions were added to excess of cold ethanol, and titrated with 0·0110N-sodium hydroxide (lacmoid). Values of k_1 were calculated by using the formula $k_1 = 2{\cdot}303\{\log_{10}[a/(a-x)]\}/t$.

Time (min.)	0	6·0	12·3	18·0	30·6	45·0	60·0	∞
Titre (ml. 0·0110N-NaOH) ...	3·41	4·69	5·82	7·01	8·93	10·85	12·50	23·34
k_1 (min.$^{-1}$)	—	0·0111	0·0105	0·0111	0·0106	0·0104	0·0102	—

To check that $Me_2C{:}CH{\cdot}CH_2{\cdot}SPh$ could not have been formed by the route $Me_2C(Cl){\cdot}CH{:}CH_2 \xrightarrow{-HCl} CH_2{:}CMe{\cdot}CH{:}CH_2 \xrightarrow{PhSH} Me_2C{:}CH{\cdot}CH_2{\cdot}SPh$, it was shown that isoprene does not add thiophenol under the conditions of the kinetic measurements. Sodium (3·25 g.) was dissolved in ethanol (100 ml.), and to the mixture were added thiophenol (15 ml.) and isoprene (10 g.). The mixture was heated at 60° for 18 hr. (sealed tube). Working up the product in the usual way gave a small amount of polymer, and a negligible quantity of material, b. p. >180°. A similar experiment was carried out with half the above quantity of sodium; the result was the same.

1-Methylallyl chloride, n_D^{25} 1·4124, was prepared as described by Catchpole and Hughes (*loc. cit.*). 1-Methylallyl phenyl sulphide was prepared by the method of Cope, Morrison, and Field (*loc. cit.*), as follows. Sodium (13·8 g.) was dissolved in absolute ethanol (600 ml.), and to the solution was added thiophenol (63 g.). The mixture was cooled to 5°, and 1-methylallyl chloride (50 g.) was added. After the mixture had been kept overnight at 5°, it was poured into water and extracted with ether. The extract was washed with sodium hydroxide solution and with water, dried ($CaCl_2$), and fractionated through a 2-ft. column packed with glass helices. The following fractions were obtained (b. p. at 2 mm.): (1) (5·0 g.), b. p. 57—58°, n_D^{25} 1·5547,* (2) (5·0 g.), b. p. 57—58°, n_D^{25} 1·5547, (3) (5·0 g.), b. p. 57—58°, n_D^{25} 1·5570, (4) (6·2 g.), b. p. 58—70°, n_D^{25} 1·5630, (5) (4·0 g.), b. p. 70°, n_D^{25} 1·5672, (6) (43·0 g.), b. p. 70°, n_D^{25} 1·5681,* residue (*ca.* 3·0 g.). The mean refractive index (1·5649) of fractions 1—6 indicates that a considerable amount of rearrangement had occurred during the fractionation. The following experiment shows that the true refractive index of the sulphide produced in the reaction is much lower. 1-Methylallyl chloride (9 g.) was added at 5° to 100 ml. of a solution of N-sodium thiophenoxide. Next morning the mixture was poured into excess of N-sodium hydroxide. The sulphides were extracted with pentane, and the pentane extract was washed with water, dried ($CaCl_2$), filtered, and distilled. When most of the pentane had been removed on a water-bath, the product was evacuated for some hours, without heating, at about 1 mm. It was then molecularly distilled from a flask at room-temperature into a trap at −80°, under the vacuum of a mercury diffusion pump. A first fraction of about 1 g., which might have had a low refractive index because of the presence of a trace of pentane, was rejected. The remainder (10 g.; n_D^{25} 1·5568) was a mixture of 1-methylallyl phenyl sulphide (84%) and but-2-enyl phenyl sulphide (16%), as judged by its refractive index. There remained a small residue (<1 g.) of undistilled solid product, probably diphenylene disulphide produced by slight oxidation of thiophenol. A similar experiment, in which the reaction was allowed to proceed at 80°, gave a product of n_D^{25} 1·5578. A sample of nearly pure 1-methylallyl phenyl sulphide, n_D^{25} 1·5555, was kept overnight at room temperature with 1·44N-sodium thiophenoxide (80 ml.). The sulphide was then recovered by the above technique, and had refractive index 1·5608.

The reaction of 1-methylallyl chloride with sodium thiophenoxide was studied kinetically in the usual way. The following are the results of an experiment at 25·0°. Portions (5·00 ml.) of the reaction mixture, initially containing 0·2266N-sodium thiophenoxide and 0·1132N-1-methylallyl chloride, were pipetted into ethanol and titrated with 0·0412N-hydrochloric acid (lacmoid indicator).

Time (min.)	0	2·92	8·73	14·80	25·28	42·40	90·1	197·0	∞
Titre (ml. 0·0412N-HCl)	27·50	27·08	26·40	25·68	24·10	23·00	20·10	16·80	13·76
k_2 (l. mole^{-1} min.$^{-1}$)	—	0·048	0·043	0·044	0·053	0·044	0·046	0·045	—

The mean velocity coefficient at 42·5° was found to be 0·252 l. mole^{-1} min.$^{-1}$, from which the energy of activation for this reaction is 18 kcal.

* There was no indication of the presence of any material intermediate in b. p. between ether and fraction 1. Cope, Morrison, and Field (*loc. cit.*) record n_D^{25} 1·5546 and 1·5680 respectively for 1-methylallyl and but-2-enyl phenyl sulphide.

The product of the reaction of 1-methylallyl chloride with sodium ethoxide in ethanol was re-examined (cf. Roberts, Young, and Winstein; Catchpole and Hughes, *locc. cit.*). 1-Methylallyl chloride (74 g.) was heated for 48 hr. at 81° with ethanolic 2N-sodium ethoxide (500 ml.) in sealed tubes. The product was poured into water and extracted six times with pentane. The pentane extracts were washed with saturated calcium chloride solution and with water, dried, and fractionated, giving the fractions: (*a*) 9·1 g., b. p. 40—75°, n_D^{25} 1·3678; (*b*) 11·5 g., b. p. 75—78°, n_D^{25} 1·3855; (*c*) 25·8 g., b. p. 78—80°, n_D^{25} 1·3862; (*d*) 3·8 g., b. p. 80—98°, n_D^{25} 1·3906; (*e*) 1·0 g., b. p. 98—101°, n_D^{25} 1·4031. By assuming that pentane, ethyl 1-methylallyl ether, and but-2-enyl ethyl ether have respectively n_D^{25} 1·3550, 1·3862,* and 1·4031,* it can be estimated that there were isolated 54·6 g. (55%) of mixed ethers containing 4·5% of but-2-enyl ethyl ether.

We are indebted to Professor E. D. Hughes, F.R.S., for valued discussions. Analyses are by Mr. A. V. Winter of this Department.

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1. [*Received, July 11th*, 1953.]

---

715. *The Addition of Free Radicals to Unsaturated Systems. Part IV.*† *The Direction of Radical Addition to Hexafluoropropene.*‡

By R. N. HASZELDINE.

The photochemical reaction of trifluoroiodomethane or of hydrogen bromide with hexafluoropropene yields only $CF_3{\cdot}[CF_2{\cdot}CF(CF_3)]_n{\cdot}CF_2{\cdot}CFI{\cdot}CF_3$ or $CF_3{\cdot}CHF{\cdot}CF_2Br$, respectively, and radical attack is thus exclusively on the CF_2 group of hexafluoropropene. Aluminium halide-catalysed addition of hydrogen bromide also yields $CF_3{\cdot}CHF{\cdot}CF_2Br$. Photochemical polymerisation of hexafluoropropene gives a trimer (a perfluorononene), a tetramer, and a pentamer.

Oxidation of the product obtained by interaction of nonafluoro-2-iodobutane and acetylene yields the acid, $C_2F_5(CF_3)CF{\cdot}CO_2H$, derivatives of which are described.

RADICAL attack on olefins of the type $R{\cdot}CH{:}CH_2$ (R = Me, Cl, F, CO_2Me, CF_3, or CN) is exclusively on the terminal methylene group, and trifluoroiodomethane, for example, yields only $CHIR{\cdot}CH_2{\cdot}CF_3$ (*J.*, 1952, 2504; 1953, 1199). The results of experiments with a perfluoro-olefin of the type $R{\cdot}CF{:}CF_2$ are now reported. Trifluoroiodomethane and hydrogen bromide were used as sources of trifluoromethyl radicals and bromine atoms, respectively, and the assumptions made have been outlined earlier (*J.*, 1952, 2504).

Attack by a Trifluoromethyl Radical.—Trifluoroiodomethane and hexafluoropropene react only slowly when exposed to light of wave-length >3000 Å, which only the fluoroiodide can absorb, and yield a compound $CF_3{\cdot}[C_3F_6]{\cdot}I$ whose constitution is described below. The reaction is faster in silica vessels, *i.e.*, with light of wave-length >2200 Å, and yields $CF_3{\cdot}[C_3F_6]_n{\cdot}I$ where $n = 1$ and 2. Spectroscopic examination shows that the nonafluoroiodobutanes are identical, *i.e.*, the direction of addition of trifluoroiodomethane is independent of the wave-length of the light used to initiate reaction.

The compound when $n = 1$ might be (I) or (II) but the following evidence shows that only (I) is formed (probably exclusively, but at least to an extent of 85%). The compound

(I) $CF_3{\cdot}CFI{\cdot}CF_2{\cdot}CF_3$ $(CF_3)_2CF{\cdot}CF_2I$ (II)

fails to react with iodine pentafluoride at 220°, but with bromine trifluoride at <0° yields perfluoro-*n*-butane (78%) which can be derived only from (I). Perfluoro-*n*-butane was synthesised from butane, perfluorobut-1-ene, and perfluorobut-2-ene by reaction with cobalt trifluoride, and from trispentafluoroethylarsine by pyrolysis, for comparison with the

* Catchpole and Hughes (*loc. cit.*) record for ethyl 1-methylallyl and but-2-enyl ethyl ether respectively n_D^{25} 1·3872 and 1·4020.

† Part III, *J.*, 1953, 1592. ‡ Presented at Amer. Chem. Soc. Meeting, Atlantic City, 1952.

product from (I). Cobalt trifluoride also reacts with (I) to give perfluoro-*n*-butane (84%); a control experiment to determine manipulation losses with the known nonafluoro-1-iodobutane [an isomer of (I)] also gave perfluoro-*n*-butane (87%). Since the yields are comparable, it is thus very probable that the compound with $n = 1$ is exclusively (I), *i.e.*, attack of the trifluoromethyl radical is entirely on the CF_2 group of hexafluoropropene with a chain mechanism of the type proposed earlier (*J.*, 1949, 2856):

$$CF_3I \xrightarrow{h\nu} CF_3\cdot + I\cdot$$

Initiation: $CF_3\cdot + CF_3\cdot CF{:}CF_2 \longrightarrow CF_3\cdot\dot{C}F\cdot CF_2\cdot CF_3$

Propagation: $CF_3\cdot\dot{C}F\cdot CF_2\cdot CF_3 + CF_3\cdot CF{:}CF_2 \longrightarrow CF_3\cdot\dot{C}F\cdot CF_2\cdot CF(CF_3)\cdot CF_2\cdot CF_3$, etc.

Transfer: $CF_3\cdot\dot{C}F\cdot CF_2\cdot CF_3 + CF_3I \longrightarrow CF_3\cdot CFI\cdot CF_2\cdot CF_3 + CF_3\cdot \longrightarrow$ etc.

In support of the above constitution, the ultra-violet spectrum of the compound where $n = 1$ shows a maximum at 280 mμ, *i.e.*, 10 mμ further to the red than would be expected for (II), which is a completely fluorinated primary iodoalkane (*J.*, 1953, 1764; see below).

Only the compound with $n = 1$ is formed in Pyrex vessels, and this is (I). The now unlikely possibility that the compound where $n = 2$ obtained in silica vessels is (IV)

(III) $CF_3\cdot CFI\cdot CF_2\cdot CF(CF_3)\cdot CF_2\cdot CF_3$ $\qquad$ $CF_3\cdot CF_2\cdot CF(CF_3)\cdot CF(CF_3)\cdot CF_2I$ (IV)

(formed by attack on the CF group of the second molecule of hexafluoropropene) can be discarded, since (I) reacts with hexafluoropropene on irradiation to give only (III), which is identical with the compound where $n = 2$:

$$(I) \xrightarrow{h\nu} (C_2F_5)(CF_3)CF\cdot \xrightarrow{C_3F_6} (C_2F_5)(CF_3)CF\cdot CF_2\cdot\dot{C}F\cdot CF_3 \xrightarrow{(C_2F_5)(CF_3)CFI} (III)$$

The compound (III) reacts with cobalt trifluoride to give perfluoro-3-methylhexane.

Since nonafluoro-2-iodobutane is the first acyclic fully fluorinated secondary iodoalkane to be reported, two free-radical reactions (with nitric oxide and acetylene) have been investigated to show its similarity to the corresponding primary iodoalkanes. Nonafluoro-2-iodobutane readily combines with nitric oxide when the mixture is irradiated in the presence of mercury (to remove any nitrogen dioxide formed) and yields the monomeric deep blue nitroso-compound (cf. *J.*, 1953, 2075). The perfluorobutyl radical also combines

$$(C_2F_5)(CF_3)CFI \xrightarrow{h\nu} (C_2F_5)(CF_3)\cdot CF\cdot \xrightarrow{NO} (C_2F_5)(CF_3)CF\cdot NO$$

with acetylene, and oxidation of the fluoroiodohexene so obtained yields hexafluoro-2-trifluoromethylbutanoic acid (cf. *J.*, 1950, 3037, 2789):

$$(C_2F_5)(CF_3)CFI \xrightarrow{h\nu} (C_2F_5)(CF_3)CF\cdot \xrightarrow{C_2H_2} (C_2F_5)(CF_3)CF\cdot CH{:}CH\cdot$$

$$(C_2F_5)(CF_3)CF\cdot CH{:}CH\cdot \xrightarrow{(C_2F_5)(CF_3)CFI} (C_2F_5)(CF_3)CF\cdot CH{:}CHI \xrightarrow{KMnO_4} (C_2F_5)(CF_3)CF\cdot CO_2H$$

This acid resembles the perfluoro-acids described in another series, and gives a methyl ester and amide in the usual way.

The photochemical polymerisation of pure hexafluoropropene is slow, and yields only products of short chain length. The main product is a trimer, C_9F_{18}, the infra-red spectrum of which reveals a strong C:C stretching vibration at 5·77 μ characteristic of the ·CF:CF· group (Haszeldine, *J.*, 1952, 4423). A ·CF:CF_2 group, which is characterised by a band at 5·56 μ (cf. $CF_3\cdot CF{:}CF_2$ 5·56, $C_2F_5\cdot CF{:}CF_2$ 5·56, $CHF{:}CF_2$ 5·56) cannot be present, but a >C:CF_2 group, which is characterised by a band at 5·71 μ [*e.g.*, $(CF_3)_2C{:}CF_2$] could be present, since replacement of a trifluoromethyl group by a perfluoroalkyl group of higher molecular weight shifts the C:C stretching vibration to slightly longer wave-length (Haszeldine and Steele, *J.*, 1953, 1592). Perfluorononenes such as $CF_3\cdot CF{:}CF\cdot CF_2\cdot CF(CF_3)\cdot CF_2\cdot CF_2\cdot CF_3$ or $CF_2{:}C(CF_3)\cdot CF_2\cdot CF(CF_3)\cdot CF_2\cdot CF_2\cdot CF_3$, produced by diradical formation from hexafluoropropene, polymerisation, and disproportionation, thus seem probable. That trimerisation did not yield perfluoro-1 : 3 : 5-trimethyl*cyclo*hexane is shown by the spectra. The poly-

meric material of higher molecular weight contains a tetramer and pentamer, probably with end groups similar to those postulated above for the trimer.

Attack by a Bromine Atom.—Hexafluoropropene and hydrogen bromide react in the dark only in presence of an aluminium halide, and give a product identical with that from the photochemical reaction. The latter reaction is slow at room temperature; bromine is liberated and dibromohexafluoropropane (2%) is formed as well as the bromohexafluoropropane. The last compound could be (V) or (VI), and that it is actually (V) (to the extent

$CF_3{\cdot}CHF{\cdot}CF_2Br$ (V) $CF_3{\cdot}CFBr{\cdot}CHF_2$ (VI) $CF_3{\cdot}CF_2{\cdot}CHFBr$ (VII)

of the least 90%) is shown by its reaction with cobalt trifluoride, since 1-bromoheptafluoropropane (80%), perfluoropropane (5%), 1 : 1 : 1 : 2 : 3 : 3 : 3-heptafluoropropane (4%), and unchanged (V) were obtained. The recovered bromohexafluoropropane was identical with the starting product, so that preferential fluorination of (V) compared with (VI) is not involved. It is noteworthy that the hydrogen atom in (V) can be replaced by fluorine without appreciable replacement of bromine by fluorine.

B. R. Steele has prepared a mixture containing (V) (85%) and (VII) (15%) by an alternative unpublished route, and comparison of the infra-red spectrum with that of the product from hexafluoropropene shows that the only common bands are those of (V); (VII) cannot be a product of the reaction of hexafluoropropene with hydrogen bromide. Furthermore, since independent evidence (see below) shows that the polarisation of hexafluoropropene is to $CF_3{\cdot}\overset{\delta-}{C}F{=}\overset{\delta+}{C}F_2$, the product formed from the aluminium halide-catalysed reaction is almost certainly (V).

These three lines of evidence, particularly the first, show that the product is (V), and that attack of the bromine atom, like that of the trifluoromethyl radical, is on the CF_2 group of hexafluoropropene:

$$HBr \xrightarrow{h\nu} H{\cdot} + Br{\cdot}$$

$$Br{\cdot} + CF_3{\cdot}CF{:}CF_2 \longrightarrow CF_3{\cdot}\dot{C}F{\cdot}CF_2Br \xrightarrow{HBr} CF_3{\cdot}CHF{\cdot}CF_2Br + Br{\cdot}$$

Discussion.—The polarisation of hexafluoropropene during reactions involving ionic intermediates is to $CF_3{\cdot}\overset{\delta-}{C}F{=}\overset{\delta+}{C}F_2$, since base-catalysed reaction with, say, ethyl alcohol proceeds as follows:

$$EtO^- + CF_2{:}CF{\cdot}CF_3 \longrightarrow EtO{\cdot}CF_2{\cdot}\bar{C}F{\cdot}CF_3 \xrightarrow{EtOH} EtO{\cdot}CF_2{\cdot}CHF{\cdot}CF_3 + EtO^- \longrightarrow \text{etc.}$$

and ammonia yields αββ-tetrafluoropropionitrile (personal communication, Minnesota Mining and Manufacturing Co.):

$$CF_3{\cdot}CF{:}CF_2 \xrightarrow{NH_3} [CF_3{\cdot}CHF{\cdot}CF_2{\cdot}NH_2] \xrightarrow{-2HF} CF_2{\cdot}CHF{\cdot}CN$$

This polarisation is the resultant of the inductive and hyperconjugative ($CF_3{\cdot}CF{:}CF_2 \longleftrightarrow \bar{F}\,CF_2{:}CF{\cdot}\overset{+}{C}F_2$) effects of the trifluoromethyl group, and of the additional effect (not found with $CH_3{\cdot}CH{:}CH_2$ and $CF_3{\cdot}CH{:}CH_2$ studied earlier) of back-co-ordination (*e.g.*, $\overset{+}{F}{:}CF{\cdot}\bar{C}F{\cdot}CF_3$). If it is again assumed (see Parts I—III) that the polarisation of the double bond when the neutral trifluoromethyl radical or bromine atom approaches is the same as in ionic reactions, it follows that radical attack takes place on the more positive carbon atom of the olefin, not the less positive as would be required if the radical were to be regarded as an electrophilic reagent. It is difficult to justify this assumption for a molecule like hexafluoropropene where various effects are operating but, since the compounds $CH_3{\cdot}CH{:}CH_2$ and $CF_3{\cdot}CH{:}CH_2$ both undergo radical attack at the terminal methylene group, it is unlikely that polar effects in the molecule play a major part in determining orientation of attack. The substituents on the carbon atoms of the double bond have a major effect on the *rate* of addition, however, and if it is assumed that the chain-transfer step is equally efficient for the reaction of trifluoroiodomethane or of hydrogen bromide with propene, 3 : 3 : 3-trifluoropropene, and

hexafluoropropene, then the ease of addition decreases in the order $CH_3{\cdot}CH{:}CH_2 \gg CF_3{\cdot}CH{:}CH_2 > CF_3{\cdot}CF{:}CF_2$.

If steric factors are neglected, and the relative stability of the possible intermediate radicals governs the orientation of attack, it follows that the secondary radicals $CF_3{\cdot}\dot{C}F{\cdot}CF_2{\cdot}CF_3$ and $CF_3{\cdot}\dot{C}F{\cdot}CF_2Br$ are more stable than the corresponding primary radicals $(CF_3)_2{\cdot}CF{\cdot}\dot{C}F_2{\cdot}$ and $CF_3{\cdot}CFBr{\cdot}\dot{C}F_2{\cdot}$ (cf. Part II, *loc. cit.*). A full discussion is deferred, but consideration of the ultra-violet spectra in the following Table is relevant.

Absorption spectra in light petroleum.

	$\lambda_{max.}$	ε	$\lambda_{min.}$	ε
$CH_3{\cdot}CH_2{\cdot}CHI{\cdot}CH_3$	261	555	219	24
$CF_3{\cdot}CH_2{\cdot}CHI{\cdot}CH_3$	267	430	218	25
$CF_3{\cdot}CH_2{\cdot}CHI{\cdot}CF_3$	270	290	224·5	26
$CF_3{\cdot}CF_2{\cdot}CFI{\cdot}CF_3$	280	220	236	50
$CF_3{\cdot}CF_2{\cdot}CF_2{\cdot}CF_2I$	271	270	215	11

The unsubstituted alkyl iodide corresponding to nonafluoro-2-iodobutane has absorption maximum at 261 mμ, and, as fluorine is introduced into the molecule, the maximum moves to longer wave-length and ε decreases. The spectrum of nonafluoro-1-iodobutane, which is typical of the fully fluorinated *n*-iodoalkanes (Haszeldine, *J.*, 1953, 1764) is included for comparison, and shows that the primary and secondary iodides can be readily distinguished by a difference in $\lambda_{max.}$ of *ca.* 10 mμ. If the interpretation of the spectra proposed earlier (*J.*, 1953, 1764) is accepted, it follows (*a*) that the radical derived from the fluoroiodo-compounds by carbon–iodine bond fission increases in stability with fluorine content, and (*b*) that the $C_2F_5{\cdot}\dot{C}F{\cdot}CF_3$ radical is more stable than the $CF_3{\cdot}[CF_2]_2{\cdot}CF_2{\cdot}$ radical; or, conversely, that the carbon–iodine bond dissociation energy is greater for fully fluorinated *n*-iodoalkanes than for the corresponding secondary iodoalkanes.

Experimental

Trifluoroiodomethane and hexafluoropropene were prepared as described earlier (*J.*, 1951, 584; 1952, 4259) and were purified in a vacuum system; their purity was checked by infra-red spectroscopic examination. Hydrogen bromide was purified and stored *in vacuo*. Precautions were taken to exclude oxygen, moisture, peroxides, etc., which might promote ionic or free-radical reactions. The reaction vessels were of Pyrex (30 ml. capacity) or silica (50-ml. capacity), and were placed 10 cm. from a Hanovia ultra-violet lamp used without the Woods filter; the reaction tubes were sealed *in vacuo*.

Reaction of Trifluoroiodomethane with Hexafluoropropene.—There was no reaction when trifluoroiodomethane (10·0 g.) and hexafluoropropene (3·0 g.) were sealed in Pyrex vessels and kept in the dark for 5 weeks. A slow reaction occurred on exposure to ultra-violet light, and after 2 weeks distillation gave unchanged reactants (90%) and a liquid, b. p. >20°, shown by infra-red spectroscopic examination to be identical with the nonafluoro-2-iodobutane described below.

A similar mixture was sealed in a silica tube, and the liquid phase was shielded from light. Exposure of the vapour to ultra-violet light for 14 days caused liberation of sufficient iodine to colour the liquid red. Distillation gave unchanged hexafluoropropene (15%, separated from trifluoroiodomethane by formation of the dibromide), trifluoroiodomethane, *nonafluoro-2-iodobutane* (94% based on C_3F_6 used), b. p. 65·5°, n_D^{20} 1·340 (Found: C, 13·9%; *M*, 346. C_4IF_9 requires C, 13·9%; *M*, 346), and material of b. p. >80° (0·1 g.). The yield of material of b. p. >80° when hexafluoropropene (3·0 g.) and trifluoroiodomethane (4·0 g.) were irradiated as above was 0·7 g. The combined material of b. p. >80° was distilled in a semi-micro apparatus, to give *dodecafluoro-2-iodo-4-trifluoromethylhexane* (0·5 g.), b. p. 136—138° (Found: C, 16·8; $C_7F_{15}I$ requires C, 16·9%), and an intermediate fraction (0·1 g.), b. p. *ca.* 120°, which is possibly 1 : 1 : 1 : 2 : 3 : 3-hexafluorodi-iodopropane (Found: C, 9·4. Calc. for $C_3F_6I_2$: C, 8·9%).

Reactions of Nonafluoro-2-iodobutane.—(a) *With hexafluoropropene.* The fluoroiodobutane (1·9 g., prepared as above) was sealed with hexafluoropropene (0·5 g.) in a 10-ml. silica tube, and irradiated for 14 days, to give dodecafluoro-2-iodo-4-trifluoromethylhexane (51%), b. p. 135—139°, shown by spectroscopic examination to be identical with the compound prepared above.

(b) *With iodine pentafluoride or bromine trifluoride.* The fluoroiodobutane (1·0 g.) was substantially unchanged after being heated with iodine pentafluoride (3 ml.) in a small autoclave at 220° for 12 hr.

To the fluoroiodobutane (1·1 g.) in a nickel tube (5 ml. capacity) cooled to −78°, was added dropwise an excess of bromine trifluoride. The volatile products were condensed, washed with 10% sodium hydroxide solution, and distilled in a vacuum system to give perfluoro-*n*-butane (78%), b. p. 1° (Found: *M*, 238. Calc. for C_4F_{10}: *M*, 238), shown by infra-red spectroscopic examination to be identical with perfluoro-*n*-butane prepared by independent routes using the cobalt fluoride method (Haszeldine and Smith, *J.*, 1950, 3617), or from trispentafluoroethylarsine by pyrolysis.

(c) *With cobalt trifluoride.* Cobalt trifluoride (100 g.) was prepared *in situ* in a 2′ horizontal copper furnace at 250—300°, and the excess of fluorine was displaced by nitrogen. Nonafluoro-2-iodobutane (3·2 g.) was added dropwise from a small dropping funnel which extended into the furnace so that the possible reaction of the fluoroiodobutane vapour with hot copper was kept to a minimum. The exit gases were condensed, washed with aqueous alkali, and distilled in a vacuum system, to give perfluoro-*n*-butane (84%) (*M*, 237), shown by its infra-red spectrum to be identical with the material prepared as above.

Reaction of Nonafluoro-1-iodobutane and of Dodecafluoro-2-iodo-4-trifluoromethylhexane with Cobalt Trifluoride.—Nonafluoro-1-iodobutane (3·0 g.), prepared from pentafluoroiodoethane and tetrafluoroethylene (*Nature*, 1950, **166**, 192), was passed over cobalt trifluoride under conditions identical with those described for nonafluoro-2-iodobutane above, to give perfluoro-*n*-butane (87%) (*M*, 238), spectroscopic examination of which showed that no rearranged product was formed.

Dodecafluoro-2-iodo-4-trifluoromethylhexane (0·9 g.) was passed over cobalt trifluoride (20 g.) in a small steel reaction vessel at 350° and gave *perfluoro-3-methylhexane* (0·2 g.), b. p. 81—82° (Found: C, 21·6%; *M*, 390. C_7F_{16} requires C, 21·7%; *M*, 388).

Hexafluoro-2-trifluoromethylbutanoic Acid.—Nonafluoro-2-iodobutane (3·2 g.) was sealed with acetylene (10% excess) and heated to 250° for 24 hr. The combined products from three such tubes were distilled, to give 3 : 4 : 4 : 5 : 5 : 5-*hexafluoro-1-iodo-3-trifluoromethylpent-1-ene* (83%), b. p. 74—76°/148 mm., 118—119°/760 mm. (micro) (Found: C, 19·2; H, 0·3. $C_6H_2IF_9$ requires C, 19·4; H, 0·8%). Oxidation of this compound (5·8 g.) by alkaline potassium permanganate and working up as described earlier (*J.*, 1950, 2789) gave, after distillation through a short column, *hexafluoro-2-trifluoromethylbutanoic acid* (51%), b. p. 135—136° (Found: C, 22·7; H, 0·3%; equiv., 265. $C_5HO_2F_9$ requires C, 22·7; H, 0·4%; equiv., 264), as a colourless, fuming liquid with an odour resembling that of heptafluorobutyric acid (*J.*, 1950, 2789). It is a strong acid, soluble in water, ethanol, acetone, and ether, and shows marked similarity in properties to heptafluorobutyric acid and to its isomer perfluoropentanoic acid.

The *methyl ester* (80% yield), b. p. 101—102° (Found: C, 26·1; H, 0·9. $C_6H_3O_2F_9$ requires C, 25·9; H, 1·1%), was converted into the *amide* (92% yield), m. p. 106—107° (Found: C, 23·0; H, 0·5; N, 5·2. $C_5H_2NOF_9$ requires C, 22·8; H, 0·8; N, 5·3%), by the methods outlined earlier (Haszeldine, *J.*, 1950, 2789; Haszeldine and Leedham, *J.*, 1953, 1548).

Nonafluoro-2-nitrosobutane.—Nonafluoro-2-iodobutane (2·1 g.) was sealed with nitric oxide (80% excess) and mercury (3 g.), and the silica tube was shaken vigorously and exposed to ultra-violet light for 8 days. Fractionation *in vacuo* gave unchanged fluoroiodobutane and *nonafluoro-2-nitrosobutane* (86% based on the fluoroiodide used, 23% on fluoroiodide taken) (Found: C, 19·0; N, 5·8%; *M*, 249. C_4NOF_9 requires C, 19·3; N, 5·6%; *M*, 249), a deep blue liquid, b. p. 23—25°.

Photochemical Polymerisation of Hexafluoropropene.—Hexafluoropropene (5·1 g.), sealed in a small silica tube so that it was mainly liquid, was exposed to ultra-violet light at a distance of 2 cm. The reaction temperature was thus *ca.* 70°. After 6 weeks, fractionation gave (*a*) unchanged hexafluoropropene (20%), (*b*) a *perfluorononene* (41%), b. p. 121—123°, n_D^{20} 1·296 (Found: C, 23·9; H, 0%; *M*, 449. C_9F_{18} requires C, 24·0; H, 0%; *M*, 450), (*c*) a fraction (*ca.* 10%), b. p. 176—180° [Found: C, 23·8. Calc. for $(C_3F_6)_4$: C, 24·0%], and (*d*) a fraction (*ca.* 10%), b. p. 215—220° [Found: C, 24·0. Calc. for $(C_3F_6)_5$: C, 24·0%]. Haszeldine and Smith (*J.*, 1950, 2689) report b. p. 124·6, n_D^{25} 1·294, for perfluoro-1 : 3 : 5-trimethyl*cyclo*hexane. The infra-red spectrum of fraction (*b*) is reported below. The spectra of fractions (*c*) and (*d*) were very similar to that of (*b*). If the hexafluoropropene is inadequately purified, or if traces of air are present during irradiation, the polymerisation is much more rapid and products are obtained which cannot be separated into clear-cut fractions.

Reaction of Hexafluoropropene with Hydrogen Bromide.—(a) *In the dark.* There was no reac-

tion when hexafluoropropene and hydrogen bromide were sealed in Pyrex and kept in the dark for 3 weeks.

(b) *In presence of aluminium halides.* Hexafluoropropene (2·1 g.), hydrogen bromide (10% excess) and aluminium bromide (0·1 g.), sealed and stored at 20° for 7 days, gave 1-bromo-1 : 1 : 2 : 3 : 3 : 3-hexafluoropropane (64%), b. p. 35·5° (Found: C, 15·5; H, 0·2%; *M*, 230. Calc. for C_3HBrF_6: C, 15·6; H, 0·4%; *M*, 231), and unchanged reactants. The yield after 3 days at 60° was 81%. Aluminium chloride gave a 70% yield after 7 days at room temperature. Park, Sharrah, and Lacher (*J. Amer. Chem. Soc.*, 1949, **71**, 2339) report b. p. 29·8—30·3°/624 mm. for the product from the catalysed vapour-phase reaction of hydrogen bromide with hexafluoropropene; the constitution of the C_3HBrF_6 was not proved by them, but was correctly inferred.

(c) *On exposure to ultra-violet light.* Hexafluoropropene (2·0 g.) and hydrogen bromide (5% excess) were sealed in a Pyrex tube and irradiated for 5 days, to give 1-bromo-1 : 1 : 2 : 3 : 3 : 3-hexafluoropropane (53%) (*M*, 230), identical with the material described above, and unchanged reactants.

A similar mixture sealed in a silica vessel was unchanged after 7 days in the dark, but after irradiation for 7 days, gave a product coloured pale-brown by bromine. The product was washed with water and distilled, to give unchanged hexafluoropropene (10%) (*M*, 150), 1-bromo-1 : 1 : 2 : 3 : 3 : 3-hexafluoropropane (88% based on hexafluoropropene taken) (*M*, 231), b. p. 35·5°, and 1 : 2-dibromohexafluoropropane (*ca.* 2%), b. p. 70—72° (*M*, 310). The identity of the products was confirmed by their infra-red spectra. Haszeldine (*J.*, 1952, **3423**) reported b. p. 71° for dibromohexafluoropropane.

Reaction of Bromohexafluoropropane with Cobalt Trifluoride.—1-Bromo-1 : 1 : 2 : 3 : 3 : 3-hexafluoropropane (3·2 g.) was passed (2 hr.) over cobalt trifluoride (100 g.) at 200°, to give (*a*) 1-bromoheptafluoropropane (80%), b. p. 12° (Found: *M*, 248. Calc. for C_3BrF_7: *M*, 249), identified, and shown to be free from its isomer, by its infra-red spectrum, (*b*) unchanged bromohexafluoropropane (5%), (*c*) 1 : 1 : 1 : 2 : 3 : 3 : 3-heptafluoropropane (*ca.* 4%), b. p. −18° (Found: *M*, 170. Calc. for C_3HF_7: *M*, 170), and (*d*) perfluoropropane (*ca.* 5%), b. p. −39° (Found: *M*, 190. Calc. for C_3F_8: *M*, 188). The infra-red spectra of (*a*), (*b*), and (*c*) showed that isomers were absent. 1-Bromoheptafluoropropane has b. p. 12° (Haszeldine, *J.*, 1952, 4259), 1 : 1 : 1 : 2 : 3 : 3 : 3-heptafluoropropane has b. p. −19° (cf. *J.*, 1952, **3423**), and perfluoropropane has b. p. −35° (Simons and Block, *J. Amer. Chem. Soc.*, 1937, **59**, 1407; 1939, **61**, 2962).

Spectra.—The infra-red spectra given in the annexed Table were recorded by a Perkin–Elmer Model 21 instrument with sodium chloride optics.

$(C_2F_5)(CF_3)$·CFI		CF_3·CHF·CF_2Br		CF_3·CFBr·CF_2Br	
4·12 (w)	9·0 (m)	3·34 (w)	8·95 (m)	4·12 (w)	8·85 } (s)
4·51 (w)	9·36 (m)	4·43 (w)	9·46 (m)	4·37 (w)	8·95 }
5·28 (w)	9·81 (m)	7·26 (m)	10·18 (s)	4·57 (w)	9·57 (s)
5·60 (w)	10·14 (m)	7·75 (s)	11·40 (m)	5·58 (w)	9·77 (s)
5·80 (w)	10·70 (s)	8·25 (vs)	11·73 (m)	6·15 (w)	9·85 (s)
6·47 (w)	11·23 (m)	8·40 (w)	11·96 (m)	6·55 (w)	10·70 (s)
6·78 (w)	11·45 (w)	8·56 (w)	12·26 (s)	6·82 (w)	10·84 (s)
7·15 (w)	11·63 (m)	8·77 (s)	14·6 (s)	7·17 (w)	11·55 (s)
7·55 (s)	12·25 (s)			7·36 (w)	12·23 (s)
7·85 (s)	13·37 } (s)			7·90 (s)	12·94 (s)
8·15 (b.v.s.)	13·46 }			8·2 (b.v.s.)	13·6 (m)
8·5 (m)	13·86 (s)			8·44 (m)	14·14 (s)
8·67 (m)	14·20 (m)			8·68 (s)	

n-C_4F_{10}			C_3F_6 trimer	
6·94 (w)	10·40 (m)		5·77 (s)	11·30 (w)
7·41 (m)	11·0 (s)		7·27 (s)	11·60 (w)
7·65 (s)	11·54 (w)		8·0 (b.v.s.)	12·05 (w)
7·97 (vs)	13·03 } (w)		8·6 (s)	12·40 (w)
8·10 (s)	13·12 }		9·67 (m)	13·5 (m)
8·35 (w)	13·62 }		9·97 (m)	13·7 (m)
8·70 (s)	13·67 } (s)		10·20 (m)	14·27 (w)
9·35 (m)	13·74 }		11·10 (w)	

b = broad, m = medium, s = strong, v = very, w = weak.

The ultra-violet spectra were measured by a Unicam Spectrophotometer.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, June 8th*, 1953.]

716. *Addition of Free Radicals to Unsaturated Systems. Part V.* The Direction of Addition to 1 : 1-Difluoroprop-1-ene, 3 : 3 : 3-Trifluoro-2-trifluoromethylprop-1-ene, and 3-Chloro-3 : 3-difluoro-2-trifluoromethylprop-1-ene.*

By R. N. Haszeldine.

Attack on 1 : 1-difluoroprop-1-ene by a CF_3 or CCl_3 radical or by a bromine atom is exclusively on the :CH· group, thus showing that radical addition can take place in the opposite direction to that predicted only from steric factors. Radical attack on $CF_3{\cdot}CR{:}CH_2$ (R = CF_3 or CF_2Cl) is on the CH_2 group. Theories of free-radical stability are discussed briefly, and in at least one example the hyperconjugative stabilisation of a radical by hydrogen on the β-carbon atom in $C{\cdot}\overset{\beta}{C}{\cdot}\overset{\alpha}{C}{\cdot}$ is shown to be of less importance than replacement of hydrogen on the α-carbon atom by any other atom or group. On this basis radical stability decreases in the order tertiary > secondary > primary, where the terms tertiary, secondary, and primary indicate the number of atoms or groups other than hydrogen attached to the α-carbon atom, *i.e.*, $\geqslant C{\cdot}$ $>CH{\cdot}$, and $-CH_2{\cdot}$, and do not necessarily refer to the carbon skeleton.

Syntheses for the olefins $CF_3{\cdot}CMe{:}CF_2$, $CCl_3{\cdot}CMe{:}CF_2$, $CClF_2{\cdot}CMe{:}CCl_2$, $CF_3{\cdot}CMe{:}CCl_2$, $(CF_3)(CClF_2)C{:}CH_2$, $(CF_3)_2C{:}CH_2$, $(CF_3)(CF_3{\cdot}CH_2)C{:}CF_2$, and $(CF_3)_2C{:}CH{\cdot}CF_3$ are presented. The polarisation of certain of these during reactions involving ionic intermediates can be represented as $CH_3{\cdot}\overset{\delta-}{C}H{=}\overset{\delta+}{C}F_2$, $CF_3{\cdot}\overset{\delta-}{C}Me{=}\overset{\delta+}{C}F_2$, $(CF_3)_2\overset{\delta-}{C}{=}\overset{\delta+}{C}H_2$, and $(CF_3)(CClF_2)\overset{\delta-}{C}{=}\overset{\delta+}{C}H_2$. New syntheses for the ketones $CF_3{\cdot}CO{\cdot}CH_3$, $CF_3{\cdot}CO{\cdot}CF_3$, and $CF_3{\cdot}CH_2{\cdot}CO{\cdot}CF_3$ are described.

In previous papers the direction of addition of a trifluoromethyl radical to the olefins $R{\cdot}CH{:}CH_2$ (R = Me, Cl, F, CO_2Me, CF_3, or CN), $CF_2{:}CClF$, and $CF_3{\cdot}CF{:}CF_2$ has been unambiguously shown to be exclusively to the $:CH_2$ or $:CF_2$ groups. A full discussion of these results has been deferred until later in this series, but as pointed out (Part III, *J.*, 1953, 1592), one explanation of the marked specificity of radical attack is that the carbon atom attacked is the one most favoured on steric grounds, *i.e.*, the terminal $:CX_2$ (X = H or F) group. There is no doubt that the steric factor is of importance, but evidence is now presented to show that radical addition can occur contrary to that predicted on steric grounds alone.

Trifluoroiodomethane reacts smoothly with 1 : 1-difluoroprop-1-ene on exposure to ultra-violet light, to give only the addition product, which might be (I) or (II). It is noteworthy that, as found with propylene (*J.*, 1953, 1199), no, or only very slight, abstraction

$CF_3{\cdot}CHMe{\cdot}CF_2I$	$CF_3{\cdot}CF_2{\cdot}CHI{\cdot}CH_3$	$CF_3{\cdot}CMe{:}CF_2$	$C_2F_5{\cdot}CH{:}CH_2$
(I)	(II)	(III)	(IV)

of allylic hydrogen atoms occurs despite the possibility for resonance stabilisation of the resultant radical ($\cdot CH_2{\cdot}CH{:}CF_2 \longleftrightarrow CH_2{:}CH{\cdot}CF_2\cdot$). That the constitution of the product is exclusively (I) follows from its ready dehydro-iodination by powdered potassium hydroxide to 1 : 1 : 3 : 3 : 3-pentafluoro-2-methylpropene (III) (83%); (II) where the iodine atom is adjacent to the pentafluoroethyl group and consequently would be difficult to remove (cf. *J.*, 1951, 2495), would have given (IV) by this procedure. The presence of the $C{:}CF_2$ group in (III) is shown by the characteristic C:C stretching absorption at 5·64 μ, and by oxidation of the olefin to trifluoroacetone. The $CH{:}CH_2$ group (cf. IV) is characterised by its C:C stretching vibration at 6·0 μ as in 3 : 3 : 3-trifluoropropene; furthermore, oxidation of (IV) is known to yield pentafluoropropionic acid and not trifluoroacetone. Examination of infra-red spectra and of the oxidation products showed that a mixture of (III) and (IV) was not present.

* Part IV, preceding paper.

Thus, with a chain mechanism of the type outlined earlier:

$$CF_3I \xrightarrow{h\nu} CF_3\cdot + I\cdot$$

Initiation: $CF_3\cdot + CH_3\cdot CH{:}CF_2 \longrightarrow CF_3\cdot CHMe\cdot CF_2\cdot$

Transfer: $CF_3\cdot CHMe\cdot CF_2\cdot + CF_3I \longrightarrow CF_3\cdot CHMe\cdot CF_2I + CF_3\cdot \longrightarrow$ etc.

it follows that attack of the trifluoromethyl radical is exclusively on the :CH· group of 1 : 1-difluoroprop-1-ene.

The reaction of bromotrichloromethane with 1 : 1-difluoroprop-1-ene is more difficult to effect than for trifluoroiodomethane, but with acetyl peroxide as initiator a 1 : 1 addition product was isolated. This was shown to be 1-bromo-3 : 3 : 3-trichloro-1 : 1-difluoro-2-methylpropane (V) by dehydrohalogenation to a mixture of (VI) and (VII), which were not separated but whose presence may be inferred since treatment of the mixture with antimony trifluorodichloride gave the known 1 : 1 : 3 : 3 : 3-pentafluoro-2-methylpropene and 1 : 1-dichloro-3 : 3 : 3-trifluoro-2-methylpropene:

$$CH_3\cdot CH{:}CF_2 \xrightarrow{CCl_3Br} \underset{(V)}{CCl_3\cdot CHMe\cdot CF_2Br} \xrightarrow{KOH\text{-}EtOH} \underset{(VI)}{CCl_3\cdot CMe{:}CF_2} + \underset{(VII)}{CCl_2{:}CMe\cdot CF_2Br}$$

$$CCl_3\cdot CMe{:}CF_2 \xrightarrow{SbF_3Cl_2} CF_3\cdot CMe{:}CF_2 \qquad CCl_2{:}CMe\cdot CF_2Br \xrightarrow{SbF_3Cl_2} CF_3\cdot CMe{:}CCl_2$$

It is also possible that (VI) might undergo allylic rearrangement to give 1 : 1 : 3-trichloro-3 : 3-difluoro-2-methylpropene in presence of antimony fluoride, and thence 1 : 1-dichloro-3 : 3 : 3-trifluoro-2-methylpropene. The ease of replacement of chlorine or bromine by fluorine shows that the halogen atoms replaced must have been allylic (cf. Haszeldine, *J.*, 1953, 3371). If the reaction of bromotrichloromethane with 1 : 1-difluoropropene had given the compound $CCl_3\cdot CF_2\cdot CHBr\cdot CH_3$, subsequent reaction with ethanolic potassium hydroxide could have removed only hydrogen bromide, to give $CCl_3\cdot CF_2\cdot CH{:}CH_2$ which, since the chlorine atoms are not allylic, could not readily yield a pentafluorobutene; nor could it yield a 1 : 1-dihalogenotrifluoro*iso*butene.

If it is assumed that the acetyl peroxide removes a bromine atom from bromotrichloromethane so that the trichloromethyl radical initiates the attack on 1 : 1-difluoropropene, the above results show that the trichloromethyl radical, like the trifluoromethyl radical, attacks the :CH· group.

The aluminium chloride-catalysed reaction of hydrogen chloride with 1 : 1-difluoroprop-1-ene yields only 1-chloro-1 : 1-difluoropropane, whose constitution follows from the boiling point (25°) (cf. $CHF_2\cdot CHCl\cdot CH_3$ 52°, $CH_3\cdot CF_2\cdot CH_2Cl$ 55°) and from the formation of only 1 : 1 : 1-trifluoropropane on treatment with antimony trifluoride. Hydrogen bromide does not react with 1 : 1-difluoropropene in the dark, and the aluminium bromide-catalysed reaction gives only 1-bromo-1 : 1-difluoropropane (b. p. 46°; cf. $CHF_2\cdot CHBr\cdot CH_3$ b. p. 72·5°, $CHF_2\cdot CH_2\cdot CH_2Br$, b. p. 93°), converted by antimony trifluoride into 1 : 1 : 1-trifluoropropane. The polarisation of 1 : 1-difluoropropene during reactions involving ionic intermediates is thus $CH_3\cdot \overset{\delta-}{C}H{=}\overset{\delta+}{C}F_2$.

The photochemical reaction of hydrogen bromide with 1 : 1-difluoropropene yields only 2-bromo-1 : 1-difluoropropane (93%). The free-radical and ionic reactions are thus very distinct and, as regards the direction of addition, the bromine atom acts like the trihalogenomethyl radicals:

$$HBr \xrightarrow{h\nu} H\cdot + Br\cdot$$

$$Br\cdot + CH_3\cdot CH{:}CF_2 \longrightarrow CH_3\cdot CHBr\cdot CF_2\cdot \xrightarrow{HBr} CH_3\cdot CHBr\cdot CHF_2 + Br\cdot \longrightarrow \text{etc.}$$

The reaction of 1 : 1 : 3 : 3 : 3-pentafluoro-2-methylpropene with hydrogen chloride is more difficult to effect than that of 1 : 1-difluoropropene, but again only one product (VIII) is formed; its constitution follows from its conversion into the known 1 : 1 : 1 : 3 : 3 : 3-hexafluoro-2-methylpropane:

$$CF_3\cdot CMe{:}CF_2 \xrightarrow{HCl} \underset{(VIII)}{CF_3\cdot CHMe\cdot CF_2Cl} \xrightarrow{SbF_3Cl_2} (CF_3)_2CHMe$$

The aluminium bromide-catalysed reaction of hydrogen bromide with pentafluoro-2-methylpropene similarly gave 1-bromo-1 : 1-difluoro-2-trifluoromethylpropane. The decreased ease of reaction with electrophilic reagents of pentafluoro-2-methylpropene relative to 1 : 1-difluoropropene is attributed to the deactivating influence of the electron-withdrawing trifluoromethyl group on the unsaturation electrons: the inductive ($F_3C \leftarrow CMe{:}CF_2$) and hyperconjugative ($F^- CF_2{:}CMe{\cdot}CF_2^+$) effects of the fluoroalkyl group, and the inductive effect of the vinylic fluorine atoms act in the same direction to give the overall polarisation $CF_3{\cdot}\overset{\delta-}{C}Me{=}\overset{\delta+}{C}F_2$ [cf. $CH_3{\cdot}CH{:}CF_2$ where the inductive and hyperconjugative effects of the CH_3 group ($CH_3 \rightarrow CH{:}CF_2$; $H^+ CH_2{:}CH{\cdot}CF_2^-$) oppose the inductive effect of the fluorine atoms].

3 : 3 : 3-Trifluoro-2-trifluoromethylprop-1-ene (IX) was synthesised as follows:

$$CF_3{\cdot}CMe{:}CF_2 \xrightarrow{Cl_2} CF_3{\cdot}CMeCl{\cdot}CF_2Cl \xrightarrow{KOH} \underset{(X)}{(CF_3)(CF_2Cl)C{:}CH_2} \xrightarrow{SbF_3Cl_2} \underset{(IX)}{(CF_3)_2C{:}CH_2}$$

Dehydrochlorination of the dichloro-compound is difficult, since the chlorine atom to be removed is adjacent to a polyfluoroalkyl group and is consequently unreactive (cf. Haszeldine, *J.*, 1951, 2459), and is best effected by solid potassium hydroxide. The product, 3-chloro-3 : 3-difluoro-2-trifluoromethyl-prop-1-ene (X) contains an allylic chlorine atom which is readily converted into a trifluoromethyl group. The hexafluoro*iso*butene (IX) was oxidised to hexafluoroacetone in neutral or acid solution, but the yield was low, since there are no halogen atoms attached directly to an olefinic carbon atom (cf. $CF_3{\cdot}CMe{:}CF_2 \longrightarrow CF_3{\cdot}CO{\cdot}CH_3$, above); the yield of hexafluoroacetone was improved by use of the sequence:

$$(CF_3)_2C{:}CH_2 \xrightarrow{Br_2} (CF_3)_2CBr{\cdot}CH_2Br \xrightarrow{KOH} (CF_3)_2C{:}CHBr \xrightarrow{KMnO_4} CF_3{\cdot}CO{\cdot}CF_3$$

The direction of ionic addition to (IX) was shown by reaction with hydrogen chloride or by aluminium bromide-catalysed reaction with hydrogen bromide:

$$(CF_3)_2\overset{\delta-}{C}{=}\overset{\delta+}{C}H_2 + HX \longrightarrow (CF_3)_2\dot{C}H{\cdot}CH_2X \quad (X = Br \text{ or } Cl)$$

The constitution of the chloro-compound follows from its synthesis by mild chlorination of 1 : 1 : 1 : 3 : 3 : 3-hexafluoro-2-methylpropane [$(CF_3)_2CH{\cdot}CH_3 \longrightarrow (CF_3)_2CH{\cdot}CH_2Cl$]; the chlorination is thus markedly directed, as for 1 : 1 : 1-trifluoropropane and similar compounds (*J.*, 1951, 2495). The constitution of the synthetic chloro-compound follows from the ease with which it is dehydrochlorinated by cold ethanolic potassium hydroxide to 3 : 3 : 3-trifluoro-2-trifluoromethylpropene: this shows that there is an acidic hydrogen atom adjacent to the perfluoroalkyl groups:

$$OH^- \quad H{-}C(CF_3)_2{-}CH_2{-}Cl \longrightarrow H_2O + (CF_3)_2C{:}CH_2 + Cl^-$$

Photochemical reaction of hydrogen bromide with (IX) at −60° (since there was a slow dark reaction at 20°) gave the same product (93%) as from the ionic reaction. 1 : 1 : 1-Trifluoropropene also gives the same product from the ionic or radical addition of hydrogen bromide (Haszeldine, *J.*, 1952, 2504).

The reaction of trifluoroiodomethane with hexafluoro*iso*butene (IX) could give (XI) or (XII). That only (XI) is formed follows from the reaction with powdered or ethanolic

$$\underset{(XI)}{(CF_3)_2CI{\cdot}CH_2{\cdot}CF_3} \qquad \underset{(XII)}{(CF_3)_2C{\cdot}CH_2I} \qquad \underset{(XIII)}{(CF_3)_2C{:}CH{\cdot}CF_3}$$

potassium hydroxide, since the known olefin 1 : 1 : 1 : 4 : 4 : 4-hexafluoro-2-trifluoromethylbut-2-ene (XIII) was produced (81%); (XII) cannot undergo intramolecular dehydroiodination. The trifluoromethyl radical, like the bromine atom, thus attacks the $:CH_2$ group of an olefin $RR'C{:}CH_2$. This conclusion is supported by the photochemical reaction of 3-chloro-3 : 3-difluoro-2-trifluoromethylprop-1-ene (X) (*i.e.*, R = CF_3, R′ = CF_2Cl) with

trifluoroiodomethane to give 1-chloro-1 : 1 : 4 : 4 : 4-pentafluoro-2-iodo-2-trifluoromethylbutane (XIV), the constitution of which followed from two reactions: (*a*) Zinc and ethanol yielded 1 : 1 : 4 : 4 : 4-pentafluoro-2-trifluoromethylbut-1-ene (XV), which on oxidation gave the known hexafluorobutan-2-one (XVI):

$$(CF_3)(CF_2Cl)C{:}CH_2 \xrightarrow[h\nu]{CF_3I} \underset{(XIV)}{(CF_3)(CF_2Cl)CI{\cdot}CH_2{\cdot}CF_3} \xrightarrow{Zn\text{–}EtOH} \underset{(XV)}{(CF_3{\cdot}CH_2)(CF_3)C{:}CF_2} \xrightarrow{KMnO_4} \underset{(XVI)}{CF_3{\cdot}CH_2{\cdot}CO{\cdot}CF_3}$$

(*b*) Dehydroiodination of (XIV) yielded (XVII) which, since it contains an allylic chlorine atom, was readily converted by antimony trifluoride into (XIII):

$$(XIV) \xrightarrow{KOH} \underset{(XVII)}{(CF_3)(CF_2Cl)C{:}CHCF_3} \xrightarrow{SbF_3Cl_2} \underset{(XIII)}{(CF_3)_2C{:}CHCF_3}$$

Discussion.—The direction of addition of a trifluoromethyl radical or of a bromine atom to olefins $R{\cdot}CH{:}CH_2$ was established earlier (Part II, *J.*, 1953, 1199), and the present work shows that for $CRR'{:}CH_2$ (R = CF_3, R′ = CF_3 or CF_2Cl) attack is again on the methylene group (to an extent of at least 80—90% and probably exclusively). Of the three theories considered earlier, the first, that a radical may be considered as an electrophilic reagent and thus adds to the more electronegative carbon atom of the olefin, may be discarded (see also Parts I—III, *locc. cit.*), if it is assumed that the polarisation of the olefin during radical attack is the same as that shown during attack by ionic reagents, *e.g.*, $RR'\overset{\delta-}{C}{=}\overset{\delta+}{CH_2}$, as above, although this theory would predict correctly for $CH_3{\cdot}\overset{\delta-}{C}H{=}\overset{\delta+}{C}F_2$.

The second theory, that radical attack is on the carbon atom most susceptible to attack on steric grounds, could explain all the results obtained hitherto, although, since fluorine is only slightly larger than hydrogen, it it difficult to account for the marked specificity of attack on an olefin such as vinyl fluoride. The results with 1 : 1-difluoroprop-1-ene reveal for the first time that addition can occur (to an extent of at least 85—95% and probably exclusively) to other than the terminal carbon atom in a system containing a terminal double bond.

The third theory—that the stability of the intermediate free radical determines the orientation in radical addition reactions—will be discussed in detail later. It may be noted at this stage, however, that the results given above show that the tertiary radicals $(CF_3)_2\dot{C}{\cdot}CH_2{\cdot}CF_3$, $(CF_3)(CF_2Cl)\dot{C}{\cdot}CH_2{\cdot}CF_3$, and $(CF_3)_2\dot{C}{\cdot}CH_2Br$ are more stable than the corresponding primary radicals $(CF_3)_3C{\cdot}CH_2{\cdot}$, $(CF_3)_2(CF_2Cl)C{\cdot}CH_2{\cdot}$, and $(CF_3)(CF_2Cl)CBr{\cdot}CH_2{\cdot}$. The results also show that the order of radical stability is not always tertiary > secondary > primary, since the primary (by carbon skeleton) radicals $CF_3{\cdot}CHMe{\cdot}CF_2{\cdot}$, $CCl_3{\cdot}CHMe{\cdot}CF_2{\cdot}$, and $CHMeBr{\cdot}CF_2{\cdot}$ are more stable than the secondary (by carbon skeleton) radicals $CH_3{\cdot}\dot{C}H{\cdot}CF_2{\cdot}CF_3$, $CH_3{\cdot}\dot{C}H{\cdot}CF_2{\cdot}CCl_3$, and $CH_3{\cdot}\dot{C}H{\cdot}CF_2Br$ (see also below).

One may regard an increase in radical stability as caused (*a*) by replacement of hydrogen attached to the carbon atom formally carrying the lone electron by *any other* atom or group, or (*b*) by the hyperconjugative stabilisation which becomes possible when hydrogen is on the carbon atom *adjacent* to that carrying the lone electron. Both effects operate in the same direction in many examples: thus the radical $(CF_3)_2\dot{C}{\cdot}CH_2{\cdot}CF_3$ could be regarded as more stable than $(CF_3)_3C{\cdot}CH_2{\cdot}$, since by (*a*) it has no hydrogen atoms attached to the carbon atoms carrying the lone electron and, by (*b*), it is stabilised by resonance forms of the type $\overset{(CF_3)_2C{:}CH{\cdot}CF_3}{H{\cdot}}$ which the second radical cannot show. For the radicals which might be formed by addition of the trifluoromethyl radical to 1 : 1-difluoropropene, however, (*a*) and (*b*) do not operate in the same sense. If (*a*) were all-important the radical $CF_3{\cdot}CHMe{\cdot}CF_2{\cdot}$ would be more stable than the radical $CH_3{\cdot}\dot{C}H{\cdot}CF_2{\cdot}CF_3$; whereas, if (*b*) were all-important, radical $CH_3{\cdot}\dot{C}H{\cdot}CF_2{\cdot}CF_3$, which has three hydrogen atoms available

for resonance stabilisation of the type H· CH_2:$CH{\cdot}CF_2{\cdot}CF_3$, would be the more stable. The experimental result indicates that $CF_3{\cdot}CHMe{\cdot}CF_2{\cdot}$ is more stable than $CH_3{\cdot}\dot{C}H{\cdot}CF_2{\cdot}CF_3$, *i.e.*, in this example at least, (*a*) is more important than (*b*). If this important postulate is adopted, *viz.*, that radical stability decreases as the number of hydrogen atoms attached directly to the carbon atom carrying the lone electron is increased, then we have, for decreasing radical stability, tertiary (*i.e.*, $\geqslant C\cdot$) > secondary (*i.e.*, $>CH\cdot$) > primary (*i.e.*, $-CH_2\cdot$), where the terms primary, secondary, and tertiary indicate not the carbon skeleton, but the *number of atoms or groups other than hydrogen* which are attached to the carbon atom formally carrying the lone electron. Into this classification fall all free radicals so far studied. There is clearly the possibility, however, that, by suitable choice of groups R and R′ in a secondary radical RR′CH·, the stability of a secondary radical can be made greater than that of a tertiary radical. Evidence that this can actually occur, and a discussion of other examples of relative radical stability, will be presented later.

Experimental

Experiments were carried out in Pyrex (30 ml.) or silica (100 ml.) tubes with stringent precautions to exclude air, moisture, etc., which might catalyse ionic or free-radical reactions. The tubes were filled from a vacuum system and sealed whilst evacuated. 1 : 1-Difluoroprop-1-ene was prepared as described earlier (Haszeldine, *J.*, 1953, 3371).

Reactions of 1 : 1-*Difluoroprop*-1-*ene.*—(a) *With trifluoroiodomethane.* A silica tube containing the olefin (4·2 g.) and trifluoroiodomethane (16·1 g.) was irradiated by a Hanovia lamp at a distance of 10 cm. for 2 weeks with the liquid phase shielded from light. Distillation then gave unchanged reactants and 1 : 1 : 1 : 3 : 3-*pentafluoro*-3-*iodo*-2-*methylpropane* (I) (77%), b. p., 95°/760 mm., 57°/200 mm., n_D^{20} 1·394 (Found: C, 17·5; H, 1·6%; *M*, 271. $C_4H_4F_5I$ requires C, 17·5; H, 1·4%; *M*, 274); fluoroform was not a reaction product, and only a small amount of iodine was liberated.

The reaction between 1 : 1-difluoroprop-1-ene (1·2 g.) and trifluoroiodomethane (4·0 g.) in a Pyrex vessel was much slower and after 2 weeks' irradiation the yield of (I) was 30%; its identity with the product obtained above was shown by comparison of infra-red spectra. It showed ultra-violet spectrum in light petroleum: $\lambda_{max.}$ 270 mμ, ε 330; $\lambda_{min.}$ 238, ε 120.

The iodo*iso*butane (3·1 g.) was dissolved in ethanol (5 ml.), cooled to 0°, and stirred; to it was added dropwise ice-cold 10% ethanolic potassium hydroxide (10% excess). Air was passed through the apparatus to sweep out evolved gases, and the reaction mixture was heated to boiling and allowed to cool. An excess of water was then added. The gaseous product was fractionated, to give 1 : 1 : 3 : 3 : 3-pentafluoro-2-methylpropene (69%), b. p. 13·8° (isoteniscope) (Found: C, 32·6; H, 1·9%; *M*, 146. Calc. for $C_4H_3F_5$: C, 32·9; H, 2·1%; *M*, 146). Henne, Shepard, and Young (*J. Amer. Chem. Soc.*, 1950, **72**, 3577) report b. p. 12·8—13·5°/745 mm. for this compound. The pentafluoro-2-methylpropene was obtained in 83% yield by addition of the iodo*iso*butane dropwise to thoroughly dried, powdered potassium hydroxide heated at 30° and later at 80°.

The decrease in b. p. of 4—5° caused by chain branching in the fluorobutenes is shown by comparison of $CF_3{\cdot}CMe$:CF_2 (13·8°, this paper) and $CF_3{\cdot}CH_2{\cdot}CH$:CF_2 (18·6°, unpublished results), and of $CF_3{\cdot}CMe$:CH_2 (6·3°; Swarts, *Bull. Soc. chim. Belg.*, 1927, **36**, 191) and of $CF_3{\cdot}CH_2{\cdot}CH$:CH_2 (10·6°; Leedham and Steele, unpublished).

(b) *With hydrogen bromide.* The olefin (1·9 g.) and anhydrous hydrogen bromide (10% excess) were sealed in a silica tube and irradiated for 4 days, with the lower half of the tube shielded from light. This irradiation time is probably longer than that necessary for complete reaction. Distillation gave 2-bromo-1 : 1-difluoropropane (93%), b. p. 72—73° (Found: *M*, 159. Calc. for $C_3H_5BrF_2$: *M*, 159). McBee, Hass, Thomas, Toland, and Truchan (*J. Amer. Chem. Soc.*, 1947, **69**, 944) report b. p. 72·6° for this compound.

Hydrogen bromide did not react with 1 : 1-difluoroprop-1-ene in the dark. When hydrogen bromide and the olefin (weights as above) were sealed with aluminium bromide (0·2 g.) and kept at 20° for 2 days the product was 1-*bromo*-1 : 1-*difluoropropane* (53%), b. p. 46—46·5° (Found: C, 22·3; H, 3·1%; *M*, 158. $C_3H_5BrF_2$ requires C, 22·6; H, 3·1%; *M*, 159), and unchanged reactants, but no material with b. p. >50°. The bromofluoropropane, sealed with antimony trifluoride (5 g.) and antimony trifluorodichloride (3 g.), and heated to 120°, gave

1 : 1 : 1-trifluoropropane (63%), b. p. −13° (Found: *M*, 98. Calc. for $C_3H_5F_3$: *M*, 98), identified spectroscopically.

(c) *With hydrogen chloride.* 1 : 1-Difluoroprop-1-ene (1·1 g.), anhydrous hydrogen chloride (30% excess), and aluminium chloride (0·01 g.) were heated to 150° for 12 hr. Distillation gave 1-chloro-1 : 1-difluoropropane (68%), b. p. 25° (isoteniscope) (Found: *M*, 113. Calc. for $C_3H_5ClF_2$: *M*, 114·5). Henne and Whaley (*ibid.*, 1942, **64**, 1157) report b. p. 25·8°. Reaction of the chlorofluoro-compound with antimony fluorides as described above gave 1 : 1 : 1-trifluoropropane, identified spectroscopically.

(d) *With bromotrichloromethane.* 1 : 1-Difluoroprop-1-ene (4·6 g.), bromotrichloromethane (20 ml.), and acetyl peroxide (0·9 g.) were shaken in a small autoclave for 18 hr. at 100°, to give unchanged fluoropropene (10%), bromotrichloromethane, and a fraction of higher b. p. which was distilled through a short column to give *1-bromo-3 : 3 : 3-trichloro-1 : 1-difluoro-2-methylpropane* (65%), b. p. 60—65°/*ca.* 0·1 mm. (Found: C, 20·8; H, 1·8. $C_4H_4BrCl_3F_2$ requires C, 20·7; H, 1·7%). To the last compound, dissolved in ethanol (20 ml.), was added with stirring a 10% excess of 10% ethanolic potassium hydroxide; the reaction was completed by heating at 40° for 10 min. The lower layer obtained by addition of an excess of hydrochloric acid was dried (P_2O_5), sealed immediately with antimony trifluorodichloride (30 g.), and, after being set aside at 20° for 12 hr., was heated to 80° for 1 hr. Distillation gave 1 : 1 : 3 : 3 : 3-pentafluoro-2-methylpropene (31%), identical with the material described above, and 1 : 1-dichloro-3 : 3 : 3-trifluoro-2-methylpropene (42%), b. p. 88—88·5° (Found: C, 26·4; H, 1·5%; *M*, 180. Calc. for $C_4H_3Cl_2F_3$: C, 26·8; H, 1·7%; *M*, 179). Henne *et al.* (*loc. cit.*) report b. p. 88·4° for the last compound.

Reactions of 1 : 1 : 3 : 3 : 3-*Pentafluoro-2-methylpropene.*—(a) *Oxidation.* The olefin (0·8 g.) was shaken with an excess of acidified potassium permanganate for 24 hr., and the mixture was then heated to 80° for 2 hr. The volatile product contained no pentafluoro-2-methylpropene. The material obtained by treatment of the aqueous phase in the usual way with sulphur dioxide, followed by ether-extraction, removal of the ether, and treatment of the residual ketone hydrate with phosphoric oxide, was combined with the volatile reaction product. Treatment with 2 : 4-dinitrophenylhydrazine gave 1 : 1 : 1-trifluoroacetone 2 : 4-dinitrophenylhydrazone (40% based on pentafluoro-2-methylpropene), m. p. 138°, identified by comparison of its spectrum with that of a known sample (Haszeldine and Leedham, *J.*, 1952, 3483); in a later experiment a specimen of the trifluoroacetone was identified by its b. p. (21°) and its infra-red spectrum.

(b) *With hydrogen chloride.* The olefin (2·1 g.) and anhydrous hydrogen chloride (50% excess) were heated stepwise during 48 hr. to 210°, to give *1-chloro-1 : 1 : 3 : 3 : 3-pentafluoro-2-methylpropane* (56%), b. p. 58—59° (Found: C, 26·2; H, 2·5%; *M*, 181. $C_4H_4ClF_5$ requires C, 26·3; H, 2·2%; *M*, 182·5), and unchanged reactants. Treatment of the product with antimony trifluorodichloride (5 g.) at 140° for 2 hr. gave 1 : 1 : 1 : 3 : 3 : 3-hexafluoro-2-methylpropane (*ca.* 70%), b. p. 20° (isoteniscope) (Found: *M*, 166. Calc. for $C_4H_4F_6$: *M*, 166). Henne *et al.* (*loc. cit.*) report b. p. 21·5°.

(c) *With hydrogen bromide.* There was no reaction when the pentafluoro*iso*butene (2·2 g.) and anhydrous hydrogen bromide (20% excess) were sealed in a silica tube and kept in the dark. Aluminium bromide (0·2 g.) was added and the resealed tube was heated to 60° for 3 hr., to give *1-bromo-1 : 1 : 3 : 3 : 3-pentafluoro-2-methylpropane* (45%), b. p. 78° (Found: C, 21·1; H, 2·0%; *M*, 225. $C_4H_4BrF_5$ requires C, 21·1; H, 1·8%; *M*, 227), and unchanged reactants. The bromo-compound (0·9 g.) gave a 69% yield of 1 : 1 : 1 : 3 : 3 : 3-hexafluoro-2-methylpropane (*M*, 166) when heated with antimony trifluorodichloride at 120°.

(d) *With chlorine.* Pentafluoro*iso*butene (2·7 g.) and a slight excess of chlorine, exposed to sunlight for 20 min., gave 1 : 2-dichloro-1 : 1 : 3 : 3 : 3-pentafluoro-2-methylpropane (100%), b. p. 75—76°, n_D^{23} 1·345 (Found: C, 22·2; H, 1·7%; *M*, 217. Calc. for $C_4H_3Cl_2F_5$: C, 22·1; H, 1·4%; *M*, 217).

The dichloro-compound (6·1 g., prepared as above) was dripped slowly on to a mass of finely powdered, anhydrous potassium hydroxide (200 g.) heated at 50° in a flask fitted with a short column and a still-head. The still-head was operated under total reflux initially, but as the temperature of the potassium hydroxide was slowly raised to 120°, the material of b. p. <60° was removed through the still-head. The total reaction time was 2 days. Redistillation gave *3-chloro-3 : 3-difluoro-2-trifluoromethylprop-1-ene* (28%), b. p. 52—55° (Found: C, 26·3; H, 1·5%; *M*, 178. $C_4H_3ClF_5$ requires C, 26·6; H, 1·1%; *M*, 180·5), which was immediately treated with antimony trifluorodichloride (20 g.) at 20° (5 hr.), then 50° (3 hr.), to give *3 : 3 : 3-trifluoro-2-trifluoromethylprop-1-ene* (93% based on the monochloro-compound), b. p. 11—13°

(isoteniscope) (Found: C, 29·5; H, 1·6%; *M*, 161. $C_4H_2F_6$ requires C, 29·3; H, 1·2%; *M*, 164). The molecular weight of this compound and vapour-pressure measurements suggest that a small amount of impurity may have been present.

Reactions of **3 : 3 : 3-*Trifluoro-2-trifluoromethylprop*-1-*ene*.**—(a) *Oxidation.* The olefin (2·3 g.) was sealed with acidified aqueous potassium permanganate and heated stepwise to 100° (25 hr.). Treatment with sulphur dioxide, followed by ether-extraction, gave, on removal of the ether, hexafluoroacetone hydrate. This was sealed with an excess of phosphoric oxide and heated to 30° (3 hr.). Fractionation *in vacuo* gave hexafluoroacetone (16%), b. p. −28°, identified by comparison of the spectra of its semicarbazone and 2 : 4-dinitrophenylhydrazone with those of known specimens. The yield of the ketone was improved (55%) when the olefin was treated with bromine and then potassium hydroxide, to give 1-bromo-3 : 3 : 3-trifluoro-2-trifluoromethylprop-1-ene, before the oxidation step.

(b) *With hydrogen bromide.* There was no reaction when the hexafluoro*iso*butene (1·5 g.) and hydrogen bromide (30% excess) were sealed in a silica tube and kept for 48 hr. at −60°, but on exposure to ultra-violet light at this temperature for 10 hr. the formation of a liquid of higher b. p. was observed, and distillation gave 2-*bromomethyl*-1 : 1 : 1 : 3 : 3 : 3-*hexafluoropropane*, (93%), b. p. 78° (Found: C, 19·5; H, 0·9. $C_4H_3BrF_6$ requires C, 19·6; H, 1·2%).

The olefin (1·5 g.), hydrogen bromide (10% excess), and aluminium bromide (0·05 g.), kept in the dark at room temperature for 8 hr., gave the same bromo-compound (81%) (Found: *M*, 240). There was a slow reaction with hydrogen bromide in the absence of the aluminium halide.

(c) *With hydrogen chloride.* The olefin (1·3 g.) and a 20% excess of hydrogen chloride were heated to 180° for 6 hr., to give 2-*chloromethyl*-1 : 1 : 1 : 3 : 3 : 3-*hexafluoropropane* (67%), b. p. 58° (Found: C, 23·7; H, 1·4%; *M*, 200. $C_4H_3ClF_6$ requires C, 23·9; H, 1·5%; *M*, 200·5).

The same chloro-compound (60%) was obtained by irradiation (2 hr.) of 1 : 1 : 1 : 3 : 3 : 3-hexafluoro-2-methylpropane (1·1 g.) and chlorine (0·5 mol.) in a silica tube, the lower portion of which was shielded and cooled to 25°. A small amount of the 1 : 1-dichloro-compound was also isolated.

(d) *With trifluoroiodomethane.* 3 : 3 : 3-Trifluoro-2-trifluoromethylprop-1-ene (2·7 g.) and trifluoroiodomethane (5·3 g.) were sealed in a silica tube and exposed to ultra-violet light for 7 days, to give unchanged reactants and 1 : 1 : 1 : 4 : 4 : 4-*hexafluoro*-2-*iodo*-2-*trifluoromethylbutane* (71%) (Found: C, 16·8; H, 0·5. $C_5H_2F_9I$ requires C, 16·7; H, 0·5%), distilled at low pressure to prevent possible decomposition (b. p. 20—21°/*ca.* 20 mm.). It was divided into two portions (i) and (ii). To (i) was added the theoretical amount of 10% ethanolic potassium hydroxide at 20° and the mixture was heated at 40° (1 hr.). The gas evolved during the reaction was collected, with the gas evolved on acidification (HCl) of the reaction medium, in a trap cooled by liquid oxygen. Portion (ii) was added dropwise to finely powdered anhydrous potassium hydroxide in a flask fitted with reflux condenser at 40°, connected to a liquid-oxygen trap. The reaction temperature was 85°. The same olefin was obtained from (i) (61%) and (ii) (81%). The two fractions were combined and redistilled, to give 1 : 1 : 1 : 4 : 4 : 4-*hexafluoro*-2-*trifluoromethylbut*-2-*ene*, b. p. 33° (Found: C, 26·1; H, 0·4%; *M*, 232. C_5HF_9 requires C, 25·9; H, 0·4%; *M*, 232), shown by its infra-red spectrum to be identical with a specimen prepared by an unambiguous route (unpublished results).

Reaction of **3-*Chloro*-3 : 3-*difluoro*-2-*trifluoromethylprop*-1-*ene with Trifluoroiodomethane*.**—The olefin (4·7 g.) was sealed with trifluoroiodomethane (8·0 g.) in a silica tube and exposed to light from a Hanovia lamp at 4 cm. distance for 7 days. The unchanged trifluoroiodomethane and olefin (27%) were removed by distillation, and the residual 1-chloro-1 : 1 : 4 : 4 : 4-pentafluoro-2-iodo-2-trifluoromethylbutane (69%) was divided into two parts.

One part was added dropwise to powdered zinc (5 g.) and refluxing ethanol (10 ml.). After 1 hr. an excess of water was added and the apparatus was swept out with nitrogen. The combined volatile product was purified in a vacuum system, to give 1 : 1 : 4 : 4 : 4-pentafluoro-2-trifluoromethylbut-1-ene (91%) (Found: *M*, 215), and this was sealed with slightly acidified (H_2SO_4) potassium permanganate solution and heated stepwise to 50° during 10 hr. The ketone was isolated as described for hexafluoroacetone and 1 : 1 : 1-trifluoroacetone above, and when treated with semicarbazide yielded 1 : 1 : 1 : 4 : 4 : 4-hexafluorobutan-2-one semicarbazone, m. p. 123° (65%) (cf. Haszeldine, *J.*, 1952, 3490).

The second portion of 1-chloro-1 : 1 : 4 : 4 : 4-pentafluoro-2-iodo-2-trifluoromethylbutane was dehydroiodinated by solid potassium hydroxide by the technique described above, but with a pressure of 400 mm. in the apparatus so that the 1-chloro-1 : 1 : 4 : 4 : 4-pentafluoro-2-trifluoromethylbut-2-ene was removed as soon as formed. The product was sealed immediately with

antimony trifluoride (10 g.) which had been activated with chlorine (20% Sb^V salts), and the mixture was heated to 40° for 1 hr. Purification of the gaseous product in a vacuum system gave 1 : 1 : 1 : 4 : 4 : 4-hexafluoro-1-trifluoromethylbut-2-ene (45%), b. p. 32—33° (Found: *M*, 230. Calc. for C_5HF_9: *M*, 232), shown by spectroscopic examination to be identical with the compound described above.

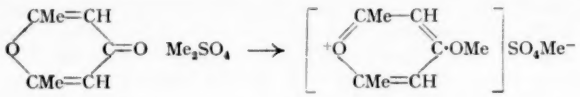
UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, June 13th*, 1953.]

717. *Trans-esterification as a Means of Halide Esterification under Neutral Conditions.*

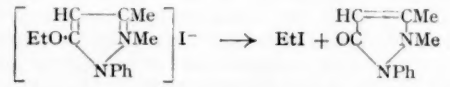
By W. M. CORBETT and J. KENNER.

A survey of the value of trans-esterification for conversion of alcohols into halide esters under neutral conditions, with arythiocarbamates as intermediaries, has indicated its inapplicability in presence of more than one ether or acetal grouping.

THE problem of esterifying alcoholic groupings in molecular structures, *e.g.*, glycosides, of which other portions are sensitive to acidic conditions, may be attacked by the procedure of double decomposition, but with only slight success. Thus the preparation of iodides from toluene-*p*-sulphonates of glycosides is limited for practical purposes to primary alcoholic groups. Although the method of direct esterification is also clearly inadmissible, the generation of the oxonium condition, on which it depends, can be achieved indirectly in a neutral medium by attack on an unsaturated system to which the oxygen atom is attached; thus, *e.g.*, dimethylpyrone yields 4-methoxy-2 : 6-dimethylpyrylium (methylsulphate) (Kehrmann and Duttendorfer, *Ber.*, 1906, **39**, 1303; Baeyer, *ibid.*, 1910, **43**, 2337):



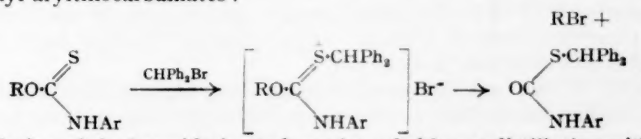
Further, Knorr recorded the thermal decomposition of 5-ethoxy-3-methyl-1-phenylpyrazole methiodide to ethyl iodide and 2 : 3-dimethyl-1-phenylpyrazolone (*Annalen*, 1896, **293**, 5, 13):



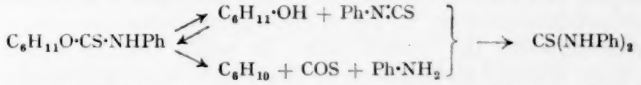
Similar relations between α- or γ-alkoxy- or -thioalkyl derivatives in the pyridine and quinoline series and corresponding *N*-methyl-pyridones or -quinolones are familiar.

These reactions illustrate the feasibility in principle of using the ester of one alcohol to esterify another irreversibly through the intermediary of a suitable unsaturated system, and we apply to such a process the term "conjugate trans-esterification," to distinguish it from the equilibration of carboxylic esters, usually connoted by "trans-esterification." The practical need of a simple preparation of the unsaturated system from the alcohol led us to select the *O*-alkyl thiocarbanilates, which are readily available from sodium alkoxides and phenyl *iso*thiocyanate (Bistryzcki, *Helv. Chim. Acta*, 1919, **2**, 131). Wheeler and Barnes (*Amer. Chem. J.*, 1900, **24**, 60) demonstrated the "conversion" of the *O*-ethyl and -*iso*butyl thiocarbanilates into their *S*-isomerides when heated with the corresponding iodide, and in other papers (*ibid.*, 1899, **22**, 141; 1900, **24**, 189, 424) analogous transformations in related types of compounds were recorded. Those authors also realised that the reactions depended on preliminary formation of a sulphonium halide. Later, Biilmann (*Annalen*, 1909, **364**, 319) recorded similar reactions in the xanthate series and found diphenylmethyl bromide to be a very effective agent in promoting, *e.g.*, the formation of ethyl bromide from *O*-ethyl *S*-carboxymethyl dithiocarbonate.

We have now found that simple *O*-alkyl phenyl- and α-naphthyl-thiocarbamates react with diphenylmethyl bromide readily in benzene, with extensive formation of *S*-diphenylmethyl arylthiocarbamates :



But, since isolation of the bromide formed was impeded by co-distillation with the solvent, it was preferable to effect the reaction at 100—120° under reduced pressure in absence of solvent. A complication arises from the tendency of thiocarbanilates to suffer reversible thermal decomposition (Hofmann, *Ber.*, 1869, **2**, 120; 1870, **3**, 172). Thus the ethyl derivative furnishes alcohol and phenyl *iso*thiocyanate: $NHPh{\cdot}CS{\cdot}OEt \rightleftharpoons EtOH + Ph{\cdot}N{:}CS$. In some instances *s*-diphenylthiourea is also formed, owing in the first place to a variant of the Tschugaeff decomposition of methyl xanthates, followed by combination of the aniline so formed with phenyl *iso*thiocyanate from the decomposition just mentioned. Thus we have found thermal decomposition of *cyclo*hexyl thiocarbanilate to yield, besides *cyclo*hexanol and diphenylthiourea, *cyclo*hexene and carbon oxysulphide :



Thiocarbamates derived from *sec.*-octyl alcohol, 2-methoxyethanol, and 1 : 3-dimethoxypropan-2-ol and, less markedly as regards diphenylthiourea formation, from 1 : 3-*O*-benzylideneglycerol behaved similarly. On the other hand, the molecular configurations of corresponding derivatives of 1 : 2-*O*-*iso*propylideneglycerol and of di-*O*-*iso*propylideneglucose, -galactose, and -mannose are unfavourable to occurrence of a Tschugaeff reaction (cf. Cram, *J. Amer. Chem. Soc.*, 1949, **71**, 3883), so that they suffered only the reversible dissociation.

The thermal effect of reaction with diphenylmethyl bromide or chloride determines the occurrence, to some extent, of the above reactions in our preparation of bromides or chlorides from the thiocarbamates. This will be apparent from the comparison of crude yields in Tables 1 and 2 with those of pure material resulting from distillation of crude product over mercuric oxide.

TABLE 1. *Reaction of thiocarbamates with diphenylmethyl bromide.*

Thiocarbamate	Bromide, % Crude	Pure	n_D	B.p./mm.	Br, % Found	Calc.
2-Methoxyethyl thiocarbanilate ...	111	90	1·4500	111·5°/771	57·7	57·5
2-Methoxy-1-methoxymethylethyl thiocarbanilate	86·5	70·5	1·4560	174·5°/763	43·7	43·8
*cyclo*Hexyl thiocarbanilate	72·5	37·8 *	1·4965	160°/751	49·3	49·1
sec.-Octyl α-naphthylthiocarbamate	75	61·5	1·4500	80·5°/27	41·1	41·4
1 : 2-*O*-*iso*Propylideneglycerol thiocarbanilate	—	21·5	1·4738	178°/756	40·7	41·0
Cholesteryl thiocarbanilate	—	47	—	(M. p. 97—98°)	—	—

* *cyclo*Hexene equivalent to 31·8% of the bromide was isolated.

TABLE 2. *Reaction of thiocarbamates with diphenylmethyl chloride.*

Thiocarbamate	Chloride, % Crude	Pure	n_D	B. p./mm.	Cl, % Found	Calc.
2-Methoxyethyl thiocarbanilate ...	85·1	75·2	1·4105	88·3°/750	37·4	37·8
2-Methoxy-1-methoxymethylethyl thiocarbanilate	92·3	57·5	1·4350	156°/750	25·1	25·6
sec.-Octyl α-naphthylthiocarbamate	—	46·5	1·4248	171°/765	23·8	23·9
1 : 2-*O*-*iso*Propylideneglycerol thiocarbanilate	—	6	1·4370	159°/759	23·5	23·6

Acetone was one of the products obtained by treating the thiocarbanilate of 1 : 2-*O*-*iso*propylideneglycerol with diphenylmethyl bromide, presumably owing to the action of

hydrogen bromide generated by some decomposition of diphenylmethyl bromide. This limits the temperature applicable to the use of the bromide with less reactive thiocarbamates, *e.g.*, of di-*O*-*iso*propylidene-glucose, -mannose, and -galactose, 1 : 3-*O*-benzylideneglycerol, and methyl 2 : 3 : 6-tri-*O*-methylglucoside, and accounts for the blackening which ensues from attempts to enforce reaction. Diphenylmethyl chloride does not suffer from this defect but is also otherwise less reactive.

(+)-*sec.*-Octyl alcohol was converted through its α-naphthylthiocarbamate into the (−)-bromide, of which the rotatory power was sensibly higher than that previously recorded, presumably because the conditions of its preparation reduced to a minimum the opportunity of racemisation by bromide ions (cf. Bergmann and Polanyi, *Naturwiss.*, 1933, **21**, 378). This result confirms the expectation that an S_N2 mechanism is involved in the above instances, and it is thus the more striking, though in accord with other expectations (cf. Barton, *J.*, 1953, 1027), that cholesterol is converted by our procedure into cholesteryl bromide without inversion of configuration.

The yield of bromide from 1 : 2-*O*-*iso*propylideneglycerol by the present method, though superior to that achieved through the toluene-*p*-sulphonate (English and Schuller, *J. Amer. Chem. Soc.*, 1952, **74**, 1361), is nevertheless very moderate. This may be due to the alternative site of attack for diphenylmethyl bromide offered by the oxygen atoms of the acetal grouping for, when the proportion of such alternatives is increased, as in 1 : 2-3 : 4-di-*O*-*iso*propylidenegalactose, 2 : 3-5 : 6-di-*O*-*iso*propylidenemannose, and 1 : 2-5 : 6-di-*O*-*iso*propylideneglucose, the method fails. As would then be expected, it is also inapplicable to the dibenzyl mercaptal of 2 : 3-5 : 6-di-*O*-*iso*propylideneglucose.

Experimental

Characteristic Data of Thiocarbamates.—These are given in Tables 3 and 4.

Table 3. *Phenylthiocarbamates* (*thiocarbanilates*).

Alcohol	M. p.	Yield, %	Formula	Found, % C	H	N	S	Required, % C	H	N	S	$[\alpha]_D^{20}$
*cyclo*Hexanol	79—80°	57	$C_{13}H_{17}ONS$	66·7	7·4	6·0	—	66·4	7·3	5·7	—	—
2-Methoxyethanol	45—46	71	$C_{10}H_{13}O_2NS$	56·8	5·7	6·7	15·6	56·9	6·2	6·6	15·1	—
1 : 3-Dimethoxypropan-2-ol	39—40	57	$C_{12}H_{17}O_3NS$	56·2	6·8	5·4	12·6	56·6	6·7	5·5	12·5	—
1 : 3-*O*-Benzylideneglycerol	158—159	—	$C_{17}H_{17}O_3NS$	65·2	5·5	4·2	9·6	64·8	5·4	4·5	10·1	—
	136—138	—	—	65·2	5·1	4·7	—					
1 : 2-*O*-*iso*Propylideneglycerol	58·5—59·5	81	$C_{13}H_{17}O_3N$	58·6	6·4	5·4	—	58·5	6·4	5·3	—	—
1 : 2-5 : 6-Di-*O*-*iso*propylidene-D-glucose	Amorphous	97	$C_{19}H_{25}O_6NS$	57·8	6·4	3·8	8·4	57·8	6·4	3·5	8·1	−49·7° ($CHCl_3$)
1 : 2-3 : 4-Di-*O*-*iso*propylidene-D-galactose	135·5—136·5	80		58·0	6·4	3·7	8·1					−76·6 ($CHCl_3$)
2 : 3-5 : 6-Di-*O*-*iso*propylidene-D-mannose	114·5—116	65	—	57·8	6·6	3·6	—					+14·8 ($CHCl_3$)
Cholesterol	179—180	44	$C_{34}H_{51}ONS$	78·8	9·9	2·9	6·3	78·5	9·9	2·7	6·1	−5·2 ($CHCl_3$)

Table 4. *α-Naphthylthiocarbamates.*

Alcohol	M. p.	Yield, %	Formula	Found, % C	H	N	Required, % C	H	N	$[\alpha]_D^{20}$
*cyclo*Hexanol	109—110°	68	$C_{17}H_{19}O_2NS$	71·5	7·1	5·0	71·6	6·7	4·9	—
sec.-Octyl alcohol	47·5—49	59	$C_{19}H_{25}ONS$	72·8	7·8	4·5	72·5	8·0	4·5	+16° (EtOH)
(+)-*sec.*-Octyl alcohol	Syrup	47				4·5				
1 : 2-5 : 6-Di-*O*-*iso*propylidene-D-glucose	Syrup	40	$C_{23}H_{27}O_6NS$	61·8	6·1	3·4	62·1	6·1	3·2	−49·3 ($CHCl_3$)
Methyl 2 : 3 : 6-trimethyl-D-glucoside	131·5—132·5	—	$C_{21}H_{27}O_6NS$	60·3	6·5	3·4	60·0	6·5	3·3	+78·6 (Me_2CO)
2 : 3-5 : 6-Di-*O*-*iso*propylidene-D-glucose dibenzylmercaptal	Syrup	69	$C_{37}H_{41}O_5NS_2$	65·9	6·0	2·1	65·8	6·1	2·1	−38·5 (C_6H_6)

Thermal Decomposition of Thiocarbamates.—*cyclo*Hexyl thiocarbanilate distils unchanged under 0·2 mm. pressure, but in an atmosphere of nitrogen at 220—240° (bath-temp.)/760 mm. it (2·808 g.) furnished a distillate from which were separated *s*-diphenylthiourea (0·297 g.), m. p. and mixed m. p. 148—149°, and fractions (*a*), a very volatile liquid (0·275 g.), b. p. 60—90°, and (*b*), *cyclo*hexanol (0·588 g.), b. p. 161—164°, n_D^{21} 1·5092 (thiocarbanilate, m. p. and mixed m. p. 77—78°). The distillate condensed by liquid air contained carbon oxysulphide, identified by sodium nitroprusside colorətion after absorption in alkali, and *cyclo*hexene (0·265 g.), b. p. 80—83°, n_D^{21} 1·4508; ψ-nitrosite, m. p. 143—144° (Wieland and Blumich, *Annalen*, 1921, **424**, 86, 88, quote m. p. 145°).

Similar results were obtained from experiments with *cyclo*hexyl α-naphthylthiocarbamate and, under reduced pressure, with *sec.*-octyl α-naphthylthiocarbamate and the thiocarbanilates of 2-methoxyethanol, 1 : 3-dimethoxypropan-2-ol, and 1 : 2-*O*-*iso*propylideneglycerol.

Thermal decomposition of 1 : 2-3 : 4-di-*O*-*iso*propylidenegalactose thiocarbanilate (3·483 g.) under 15 mm. pressure of nitrogen at 220° (bath-temp.) yielded a distillate from which were separated (*a*) phenyl *iso*thiocyanate (0·989 g.), b. p. 130° (bath-temp.)/19 mm., n_D^{23} 1·6445, characterised as *s*-diphenylthiourea, m. p. and mixed m. p. 154—155°, and (*b*) di-*O*-*iso*propylidene galactose (1·785 g.), b. p. 140° (bath-temp.)/0·03 mm., n_D^{23} 1·4672, $[\alpha]_D^{20}$ −59·6° (*c*, 1·74 in $CHCl_3$) (acetate, m. p. 108—109°). No carbon oxysulphide could be detected by absorption in alkali. The thiocarbanilates of 1 : 3-dimethoxypropan-2-ol, 1 : 3-*O*-benzylideneglycerol (both modifications), 1 : 2-5 : 6-di-*O*-*iso*propylideneglucose, and 2 : 3-5 : 6-di-*O*-*iso*propylidenemannose yielded similar results.

Treatment of Thiocarbamates with Diphenylmethyl Bromide.—The distillate obtained by heating a mixture of the thiocarbamate with 1 mol. of the bromide at 120—130°/15 mm. was collected in a receiver cooled by liquid air and redistilled over mercuric oxide or potassium permanganate to remove sulphur-containing impurities. The residue from the first distillation was *S*-diphenylmethyl thiocarbanilate or α-*naphthylthiocarbamate*; after recrystallisation from alcohol, these had, respectively, m. p. 138—139·5° (Becker and Bistryzcki, *loc. cit.*, quote m. p. 135—136°) (Found: N, 4·5; S, 9·5. Calc. for $C_{20}H_{17}ONS$: N, 4·4; S, 10·0%), and m. p. 162—163° (Found: C, 77·6; H, 5·4; N, 4·1; S, 8·8. $C_{24}H_{19}ONS$ requires C, 78·0; H, 5·2; N, 3·8; S, 8·7%).

Cholesteryl bromide was isolated (after fusion of a mixture of the thiocarbanilate with the bromide for 1 hr. at 120°) by recrystallisation from alcohol.

The respective yields and physical and analytical data are summarised in Table 1. The crude *cyclo*hexyl bromide contained *cyclo*hexene, b. p. 83°, n_D^{22} 1·44501, and carbon oxysulphide was detected in the gaseous distillate.

Non-reactivity with the bromide of thiocarbamates already cited was shown by observation of the rotatory power of the reactant mixture in benzene where this was not inhibited by darkening, or by recovery in good yield of the unchanged material from solution or mixture after fusion at 120°.

Treatment of Thiocarbamates with Diphenylmethyl Chloride.—A similar procedure with diphenylmethyl chloride afforded the products whose relevant physical and analytical data are shown in Table 2.

We are pleased to acknowledge our indebtedness to Dr. R. Merian who contributed numerous preliminary experiments. This work forms part of the programme of fundamental research undertaken by the Council of the British Rayon Research Association.

The British Rayon Research Association,
Barton Dock Road, Urmston, Nr. Manchester. [*Received, June 25th*, 1953.]

718. *Studies of N-Halogeno-compounds. Part V.* The Interaction of Dialkylchloramines with Phenols.*

By L. O. Brown and F. G. Soper.

Solutions of diethylchloramine and phenols interact in the main by a direct mechanism and not by preliminary hydrolysis of the chloramine to hypochlorous acid. The kinetics can be interpreted in terms of interaction of phenoxide ions and diethylchlorammonium cations. Such active species are in harmony with an observed constant rate of interaction over a wide range of pH, decreasing both in more strongly acid and in more strongly alkaline solution. From the kinetic data, the acid ionisation constant of the diethylchlorammonium cation is 0·09. Its reactivity towards phenols is approximately 10^3 times that of hypochlorous acid, whilst hypochlorous acid is some 10^3 times as reactive as a chlorinating agent towards phenol (Hurst and Soper, *J.*, 1949, 107) as is *N*-chloroacetanilide. Unlike *N*-chloroacetanilide, which hydrolyses to hypochlorous acid at a rate proportional to the hydroxyl-ion concentration, diethylchloramine hydrolyses at a rate apparently independent of the alkalinity.

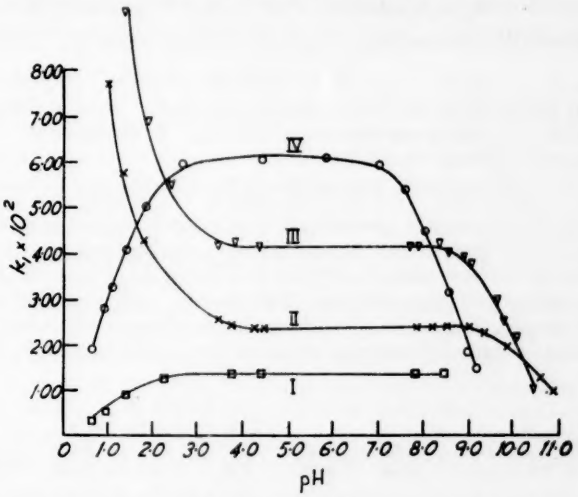
The interaction of *N*-chloroacetanilide with phenols was shown by Hurst and Soper (*loc. cit.*) to be due to two concurrent reactions: (*a*) a rate of hydrolysis of the chloramine to hypochlorous acid dependent on the hydroxyl-ion concentration and independent of the phenol concentration, and (*b*) a direct chlorination of the phenoxide ion by the chloramine molecule acting as an electrophilic substituting reagent. It may be expected that the reactivity of a chloramine as an electrophilic chlorinating agent will be related to the ease of separation of positive chlorine from it, and this in turn should parallel the ease of proton release from the parent amine or amide. Hence the more acidic the amine or amide the more reactive should be its chloramine as an electrophilic chlorinating agent in direct chlorinations and, in comparison with *N*-chloroacetanilide, the dialkylchloramines should be much less effective as direct chlorinating agents. Contrary to expectation, however, their kinetic behaviour towards phenol indicated a high mutual reactivity which was constant over a wide range of pH. Decreased activity was observed in alkaline solutions and, for some phenols, also in more strongly acid solutions.

The solutions of dialkylchloramines were prepared by addition of hypochlorous acid to a slightly alkaline solution of the dialkylammonium chloride. Absorption spectra showed that no detectable free hypochlorous acid was present, and that no alkyldichloramine was formed by dealkylation. There was no loss of oxidising titre of the hypochlorous acid in the formation of the chloramine. Examination of the stability of diethyldichloramine solutions was made by observation of the ultra-violet spectrum of the chloramine (Metcalf, *J.*, 1942, 148), which was unchanged over the pH range 2—13 and quite distinct from that or hypochlorite (Corbett, Metcalf, and Soper, *J.*, 1953, 1927). There was no appreciable formation of hypochlorite by the reaction $Et_2NCl + NaOH = NaOCl + Et_2NH$ even in 0·5N-sodium hydroxide, although under similar conditions chloramine is appreciably converted into hypochlorite. In these alkaline solutions the ultra-violet spectrum of dialkylchloramine was unchanged. The diethylchloramine was also stable in sulphuric acid solution at pH 2 for at least 3 hr.

The rate of reaction between the dialkylchloramine and phenol was examined in a series of buffered aqueous solutions at 25·0°, the phenol solution being added last to initiate the reaction. The rate of chlorination of the phenol or disappearance of the chloramine was measured by addition of aliquots to acidified potassium iodide solution and titration of the liberated iodine with thiosulphate. In the presence of excess of phenol the rate followed a first-order equation, and was not appreciably affected by the concentration of the boric acid buffer. Typical results are given in Table 1, k_1 being in min.$^{-1}$; they indicate that k_1, given by $v = k_1[R_2NCl]$, is, to a first approximation, proportional to the total phenol present and apparently is unaffected by the proportion of phenol in

* Part IV, *J.*, 1953, 1927.

the form of the more reactive phenoxide ion. In contrast to this behaviour of diethylchloramine, *N*-chloroacetanilide was found by Hurst and Soper (*loc. cit.*) to become increasingly reactive with increasing alkalinity owing to (1) increased rate of hydrolysis to hypochlorous acid and (2) increased direct reaction with the increased fraction of phenol in the form of phenoxide ion. In further contrast diethylchloramine becomes less reactive to phenol in the more alkaline solutions, as is shown in Table 2, in which k_2 is given by $v = k_2[\mathrm{PhOH}][\mathrm{R_2NCl}]$ and is related to k_1 by the equation $k_2 = k_1/[\mathrm{PhOH}]$. Here [PhOH] represents the un-ionised phenol present in the solution, K_a', the ionisation constant of phenol, being taken as $1{\cdot}1 \times 10^{-10}$. Similar results were obtained in alkaline solutions with *o*- and *p*-chlorophenol and *p*-cresol (see Figure). In all cases the specific rate,



I, 0·04M-p-*Chlorophenol.*
II, 0·04M-p-*Cresol.*
III, 0·08M-*Phenol.*
IV, 0·04M-o-*Chlorophenol.*

k_1, diminished in more alkaline solutions as though the chloramine were capable of reacting with the phenol and incapable of reacting with the more reactive phenoxide ion, into which the phenol is converted in alkaline solution. Such an explanation would be contrary to experience, when the attacking chlorinating reagent is electrophilic.

An alternative explanation of the kinetic behaviour is that the reaction occurs

TABLE 1.

$[\mathrm{Et_2NCl}] = 0{\cdot}0075$M. Boric acid buffer = 0·05M (calc. on H_3BO_3).

pH	8·79	8·98	9·24
[Phenol], M	$100k_1$	$100k_1$	$100k_1$
0·02	1·05	1·02	0·98
0·04	1·87	1·88	1·80
0·08	3·61	3·66	3·44
0·20	8·77	8·52	8·04
$100[\mathrm{PhO^-}]/[\mathrm{PhO^-} + \mathrm{PhOH}]$	5·3	9·5	16·0

TABLE 2.

Phenol = 0·08M.

pH	8·04	8·98	9·24	9·53	9·76	9·99	10·22	10·51
$100\,k_1$, min.$^{-1}$	4·01	3·66	3·44	2·83	2·38	2·00	1·43	0·92
$100\,[\mathrm{PhOH}]/[\mathrm{PhOH} + \mathrm{PhO^-}]$	98·8	90·5	84·0	72·9	61·4	48·3	35·5	21·9
k_2, min.$^{-1}$ moles l.$^{-1}$	0·508	0·505	0·513	0·487	0·486	0·519	0·507	0·523

between protonated dialkylchlorammonium ion and the phenoxide ion, *i.e.*, $v = k_3[\mathrm{R_2NHCl^+}][\mathrm{PhO^-}]$. Comparison with k_2 shows that

$$k_3 = k_2[\mathrm{PhOH}][\mathrm{R_2NCl}]/[\mathrm{R_2NHCl^+}][\mathrm{PhO^-}] = k_2K_a''/K_a'$$

where $K_a'' = [\mathrm{H^+}][\mathrm{R_2NCl}]/[\mathrm{R_2NHCl^+}]$. Hence, constant values of velocity coefficients k_2, based on the unlikely assumption of a reaction between un-ionised phenol and chloramine,

must result in constant values of k_3 based on an interaction of phenoxide ions with the dialkylchlorammonium ions. Such molecular species will be highly reactive towards each other.

Behaviour in acid solution. Since $[PhO^-] = K_a'[PhOH + PhO^-]/(K_a' + [H^+])$ and $[R_2NHCl^+] = [H^+][R_2NHCl^+ + R_2NCl]/(K_a'' + [H^+])$, we have

$$v = k_3[PhO^-][R_2NHCl^+]$$
$$= k_3[PhOH + PhO^-][R_2NHCl^+ + R_2NCl] \,.\, K_a'[H^+]/\{(K_a' + [H^+])(K_a'' + [H^+])\}$$

Further, since k_1 is evaluated in the presence of excess of phenol by the equation

$$v = k_1[R_2NHCl^+ + R_2NCl],$$
$$k_1 = k_3[PhOH + PhO^-] \,.\, K_a'[H^+]/\{(K_a' + [H^+])(K_a'' + [H^+])\}$$

It folows that in solutions of medium acidity, where $K_a'' \gg [H^+] \gg K_a'$,

$$k_1 = k_3[PhOH] \,.\, K_a'/K_a'' = \text{constant}$$

In highly acid solutions, where $[H^+] \gg K_a'$, $k_1 = k_3[PhOH] \,.\, K_a'/(K_a'' + [H^+])$ and when $[H^+]$ becomes commensurate with K_a'', k_1 diminishes. Finally, in alkaline solutions, where K_a'' and $K_a' > [H^+]$,

$$k_1 = [PhO^- + PhOH][H^+]/k_3K_a'' = \text{constant} \times [H^+] = \text{constant}/[OH^-]$$

Hence, for a constant concentration of a particular phenol, k_1 should be constant over a range of pH, diminishing in more strongly alkaline and also in more strongly acid solutions. Values for *o*-chlorophenol are shown in Table 3. For work in acid solutions, the diethylchloramine was prepared from diethylamine and hypochlorous acid free from chloride. Such preparations of diethylchloramine duplicated the behaviour in neutral and alkaline solution of diethylchloramine prepared from diethylamine hydrochloride and hypochlorous acid.

TABLE 3.

o-Chlorophenol = 0·04M.

pH	1·08	1·80	2·22	4·41	6·03	7·06	8·03	8·53	9·10
$k_1 \times 10^3$	3·14	4·96	5·44	5·93	5·94	5·94	4·31	2·98	1·30

A similar decrease in speed is observed in the case of *p*-chlorophenol with increasing acidity, as shown in the Figure. For the more easily chlorinated phenol and *p*-cresol, the rate increases with increasing acidity. This may possibly be due to the development of chlorine in the solution, or alternatively to the fact that, with these phenols, the dialkylchlorammonium ion can substitute both the phenoxide ion and the un-ionised phenol, the latter reaction becoming the more important and dominating in the more acid solutions. If the enhanced reactivity were due to the development of chloride and the formation of chlorine by the reaction, $H^+ + Cl^- + Et_2NCl = Cl_2 + Et_2NH$, the observed rates would be due to the chance impurity of chloride ion and would not be reproducible whereas duplicate experiments carried out at different times gave concordant results. Hence it is considered that the dialkylchlorammonium ion can chlorinate both the phenoxide ion and the un-ionised phenol in the more reactive phenols.

The observed higher reactivity of *o*-chlorophenol than of phenol in the plateau region of the graph is additional confirmation of a mechanism involving phenoxide ions, the higher ionisation constant of the chlorophenol providing a higher concentration of the reactive ion.

Ionisation constant of the dialkylchlorammonium ion. The decrease in reactivity in more acid solutions of the chlorophenols, if these phenols react with diethylchloramine by the mechanism involving the phenoxide ion only, can be related to the ionisation constant K_a''' of the equilibrium, $Et_2NHCl^+ \rightleftharpoons H^+ + Et_2NCl$. Since in acid solutions

$$k_1 = k_3[PhOH]K_a'/(K_a'' + [H^+])$$

and since the condition for the plateau part of the reactivity curve is that $K_a'' \gg [H^+]$, the specific rate, k_1, is reduced to half the plateau value when $[H^+] = K_a''$. This reduction of k_1 to half the plateau value occurs at approximately pH 1 for both *o*- and *p*-chlorophenol, indicating that K_a'' is approximately 0·1 (actual values 0·098 and 0·080).

Rate of hydrolysis of diethylchloramine. In the interaction of *N*-chloroacetamide with phenol (Hurst and Soper, *loc. cit.*) it was found that, whilst the chloramine could react directly with the phenoxide ion, there occurred a simultaneous reaction of zero order with regard to phenol concentration. This was due to the hydrolysis $PhAcNCl + OH^- = PhAcNH + OCl^-$. Similar hydrolysis might be expected of the dialkylchloramines and may be expressed as a phenol-independent term in the rate equation $k_1 = k_0 + k_2$[total phenol]. A plot of the values of k_1 given in Table 1 against [total phenol] at the pH's of 8·79, 8·98, and 9·24 gave intercepts for $100k_0$ of 0·19, 0·24, and 0·22 min.$^{-1}$, respectively, indicating that for diethylchloramine the hydrolysis rate appears to be independent of pH. To examine this conclusion further, the rates of a series of reactions at pH 4·4 were measured, various *p*-cresol concentrations being used. The results, shown herewith, gave a similar value for the hydrolysis rate k_0, *viz.*, $0·25 \times 10^{-2}$ min.$^{-1}$. The mean rate k_0 is $0·225 \times 10^{-2}$ min.$^{-1}$.

[*p*-Cresol]	0·016	0·024	0·040	0·080
$k_1 \times 10^2$, min.$^{-1}$	1·04	1·45	2·28	4·26
$k_1 \times 10^2$, min.$^{-1}$ = 0·25 + 50·0[total phenol]	1·05	1·45	2·25	4·25

Two hydrolysis mechanisms conform to a rate of production of hypochlorous acid which is independent of pH. The alternative mechanisms are (*a*) an interaction of diethylchloramine and water (cf. Sidgwick, "Chemical Elements and Compounds," Oxford University Press, 1950, p. 704, on the hydrolysis of nitrogen trichloride) or (*b*) an interaction of diethylchlorammonium ion and hydroxyl ion. Such alternatives cannot be differentiated by rate measurements.

The hydrolysis constant of diethylchloramine. The hydrolysis constant of chloramine (Corbett, Metcalf, and Soper, *J.*, 1953, 1927) is $2·8 \times 10^{-10}$ at 15°. Diethylamine being a stronger base than ammonia, *i.e.*, the amine cation being a weaker acid than NH_4^+, one would expect the hydrolysis of diethylchloramine to be less than that of chloramine.

Since both the rate of formation of diethylchloramine from diethylamine and hypochlorous acid (Edmond and Soper, *loc. cit.*) and now the rate of hydrolysis of diethylchloramine are known, an estimate can be made of the hydrolysis constant of the reaction :

$$Et_2NCl + H_2O \underset{k_2}{\overset{k_0}{\rightleftharpoons}} Et_2NH + HOCl$$

This hydrolysis constant, $K_h = [Et_2NH][HOCl]/[Et_2NCl] = k_0/k_2$. The rate of formation of diethylchloramine is given by $v = k_{2(obs.)}$[total HOCl][total amine], and at pH 2·3—3·5, $v = k_{2(obs.)}[HOCl][Et_2NH_2^+]$, as practically all the hypochlorous acid is un-ionised and the amine is present as cations. The relation of $k_{2(obs.)}$ to k_2, defined by $v = k_2[HOCl][Et_2NH]$, is that $k_2 = k_{2(obs.)}[Et_2NH_2^+]/[Et_2NH] = k_{2(obs.)}K_b''/[OH^-]$. The ratio $k_{2(obs.)}/[OH^-]$ over the pH range 2·31—3·51 was found to be constant and equal to $9·53 \times 10^{11}$ min.$^{-1}$ moles^{-2} l.^{2}, whence $k_2 = 9·53 \times 10^{11} \times 1·26 \times 10^{-3}$ and $K_h = k_0/k_2 = 0·225 \times 10^{-2}/9·53 \times 10^{11} \times 1·26 \times 10^{-3} = 2·0 \times 10^{-12}$. This value of K_h is of the right order of magnitude, and some confirmation of it is given by work of L. C. Baker (University of New Zealand, Thesis, 1941) on the equilibrium $Et_2NCl + NH_3 \rightleftharpoons NH_2Cl + Et_2NH$, spectrophotometric studies of which gave an equilibrium constant at room temperature of $3·5 \times 10^{-2}$. This constant is the ratio of the hydrolysis equilibrium constants of (*a*) $Et_2NCl + H_2O \rightleftarrows HOCl + Et_2NH$ and (*b*) $NH_2Cl + H_2O \rightleftarrows HOCl + NH_3$, and the value of the latter (Corbett, Metcalfe, and Soper, *loc. cit.*) is $2·8 \times 10^{-10}$ at 15°. This gives a value for the diethylchloramine hydrolysis constant of $9·8 \times 10^{-12}$. The comparison with the ratio of the two specific rate constants is not unsatisfactory when it is borne in mind that the rate constant of formation was determined at pH 2·3—3·5 and that of the hydrolysis at pH 4·4 and 8·8—9·2.

Relative reactivities of the phenoxide ions with the dialkylchloramine ion. From the foregoing evidence, the rate of interaction of diethylchloramine and phenol can be represented as a sum of two rates :

$$\begin{aligned} v = k_1[\text{chloramine}] &= k_0[\text{chloramine}] + k_2[\text{chloramine}][\text{phenol}] \\ &= k_0[\text{chloramine}] + k_3[PhO^-][R_2NHCl^+] \end{aligned}$$

i.e., $$k_1 - k_0 = k_3[PhOH + PhO^-] \,.\, K_a'[H^+]/\{(K_a' + [H^+])(K_3'' + [H^+])\}$$

and at the flat portion of the curve $k_1 - k_0 = k_3[\mathrm{PhOH}]K_a'/K_a''$, whence k_3 can be calculated. The value of K_a'' being taken as 0·09, the reactivities k_3 of the various phenoxide ions towards the dialkylchlorammonium ion are given below. In this Table

Phenol	Concn., M	$(k_1 - k_0) \times 10^2$	$K_a' \times 10^{10}$	$k_3 \times 10^{-8}$	$k \times 10^{-5}$ *
p-Cresol	0·04	2·06	0·67	7·7	9·0
Phenol	0·08	3·84	1·3	3·93	3·3
o-Chlorophenol	0·04	5·72	7·7	1·67	0·59
p-Chlorophenol	0·04	1·02	4·1	0·56	0·49

* Chlorination of phenols by hypochlorous acid, Soper and Smith, *J.*, 1926, 1589.

the phenols fall into an order of reactivity given by the values of k_3 similar to that observed in the substitution of phenols by hypochlorous acid. This rate constant k_3 interprets the kinetics in terms of interaction between dialkylchlorammonium ions and phenoxide ions and explains the anomaly that over a wide range of pH (see Figure) the apparent reactivity of *o*-chlorophenol towards a chloramine is greater than that of *p*-cresol. The effectiveness of the diethylchlorammonium cation as a chlorinating agent is approximately 1000 times greater than that of hypochlorous acid, whilst *N*-chloroacetanilide (Hurst and Soper, *loc. cit.*) chlorinates phenol some 1000 times less rapidly than the hypochlorous acid.

UNIVERSITY OF OTAGO, DUNEDIN, NEW ZEALAND. [*Received, May 18th*, 1953.]

---

719. *The Oxidation of Carboxylic Acids containing a Tertiary Carbon Atom. Part II.**

By J. KENYON and M. C. R. SYMONS.

Two procedures have been described in Part I * whereby branched-chain carboxylic acids $RR'CH{\cdot}[CH_2]_n{\cdot}CO_2H$ are converted into the corresponding hydroxy-acids $RR'C(OH){\cdot}[CH_2]_n{\cdot}CO_2H$, the prescribed oxidants being (*a*) potassium permanganate in concentrated alkaline solution ($n = 0$ or 2) and (*b*) potassium manganate in dilute alkaline solution ($n = 2$). Applied to optically active carboxylic acids, oxidations by method (*a*) result in complete loss of optical activity, whereas those by method (*b*) result in complete retention of activity. It is postulated that the radical ion $RR'\dot{C}{\cdot}[CH_2]_n{\cdot}CO_2^-$ and the lactone $RR'\dot{C}{\cdot}[CH_2]_2{\cdot}\dot{C}O_2$ are the respective intermediates in these reactions which, together, constitute an example of an oxidation which may proceed either by a single two-electron change or by two consecutive one-electron changes.

THE behaviour of several optically active branched-chain carboxylic acids of type $RR'CH{\cdot}[CH_2]_n{\cdot}CO_2H$, in which $n = 0$ or 2, R = Me, and R' = Et or Ph, when subjected to oxidation by (*a*) potassium permanganate in concentrated alkaline solution and (*b*) potassium manganate in dilute alkaline solution, has been studied. In Part I,* it was reported that the use of permanganate afforded good yields of the corresponding hydroxy-acids $RR'C(OH){\cdot}[CH_2]_n{\cdot}CO_2H$ when $n = 0$ or 2, whilst the use of manganate led to good yields of the corresponding hydroxy-acids, when $n = 2$. It is now shown that the products obtained from optically active acids by oxidation with permanganate are devoid of optical activity, whereas with manganate there is no loss of activity. Since both reactants and products are optically stable in hot concentrated alkaline solution, the two reactions must proceed by different mechanisms.

There is considerable evidence (contributed largely by McKenzie *et al.*) that extensive racemisation occurs during the alkaline hydrolysis of α-substituted carboxylic esters, and

* The communication "The Oxidation of Carboxylic Acids containing a Tertiary Carbon Atom," *J.*, 1953, 2129, is regarded as Part I.

Kenyon and Young (*J.*, 1940, 216) have found that such esters readily racemise in the presence of sodium ethoxide. This racemisation, which may be a consequence either of the formation of the ion $RR'\bar{C}\cdot CO_2Et$ or of a series of inversions in which the solvent participates (Dewar, "Electronic Theory of Organic Chemistry," Oxford Univ. Press, London, 1949, p. 110), is not observed when optically active branched-chain carboxylic acids are heated for several hours in concentrated alkaline solution. This precludes any mechanism involving an initial ionization of the type:

$$RR'CH\cdot[CH_2]_n\cdot CO_2^- + OH^- \longrightarrow RR'\bar{C}\cdot[CH_2]_n\cdot CO_2^- + H_2O$$

followed by an electron-transfer reaction as postulated by Drummond and Waters (*J.*, 1953, 435) for oxidations by alkaline permanganate. It may, therefore, be concluded that the first step in either mechanism is an attack by the oxidant at the "tertiary" hydrogen atom, leading to its removal as an atom or negative ion. Removal of hydrogen as an atom would result in the radical ion $RR'\dot{C}\cdot[CH_2]_n\cdot CO_2^-$ becoming kinetically free during the reaction, with consequent extensive racemisation. Since, in reactions with permanganate the oxidant undergoes a one-electron change and the hydroxy-acids obtained are devoid of optical activity, it is postulated that such reactions proceed by a free-radical mechanism.

On the other hand, removal of hydrogen, together with both its bonding electrons, would result in formation of a zwitterion of type $RR'\overset{+}{C}\cdot[CH_2]_n\cdot CO_2^-$. The behaviour of optically active halogeno-carboxylic acids (Hughes, *Quart. Reviews*, 1951, **5**, 255) shows that the formation of an intermediate of this type results in complete inversion of configuration about the positive carbon atom. Since, during reactions with manganate, the oxidant undergoes a two-electron change and there is no loss of optical activity during the reaction, it is concluded that these oxidations probably proceed by this alternative mechanism.

Discussion.—Reactions between branched-chain carboxylic acids and permanganate in dilute alkaline solution are slow, even at elevated temperatures, and result in extensive degradation of the acid: when the concentration of alkali is high, the reaction is rapid, proceeds at room temperature, and leads to hydroxy-acids, which are not further attacked. Although it is possible that the change in mode of reaction is due to the stabilisation of the manganate ion by the alkali, this can hardly account for the marked change in the rate of oxidation. It may be that a new mode of attack is involved which is related to the large increase in the rate of decomposition of permanganate with increase in concentration of alkali:

$$4KMnO_4 + 4KOH \longrightarrow 4K_2MnO_4 + 2H_2O + O_2$$

It has been postulated that the first stage in this decomposition involves the formation of a free hydroxyl radical:

$$MnO_4^- + OH^- \longrightarrow MnO_4^{2-} + \cdot OH$$

(Stamm, "Newer Methods of Volumetric Chemical Analysis," transl. by Oesper, Van Nostrand Co. Inc., New York, 1938; Symons, *Research*, 1953, **6**, 5S), and a recent kinetic study (*J.*, in the press) supports the view that this primary step is followed by the formation of the $\cdot O^-$ radical ion:

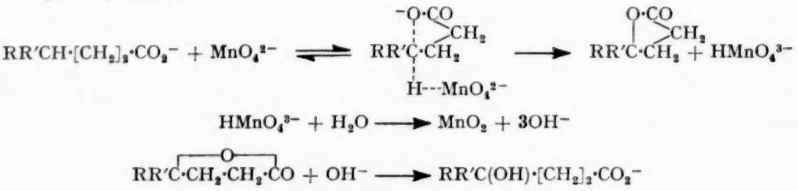
$$\cdot OH + OH^- \rightleftharpoons \cdot O^- + H_2O$$

Accordingly, it is postulated that for reactions with permanganate, the active oxidant is the free hydroxyl radical or the $\cdot O^-$ radical ion:

$$RR'CH\cdot[CH_2]_n\cdot CO_2^- + \cdot OH \longrightarrow RR'\dot{C}\cdot[CH_2]_n\cdot CO_2^- + H_2O$$
$$RR'\dot{C}\cdot[CH_2]_n\cdot CO_2^- + \cdot OH \longrightarrow RR'C(OH)\cdot[CH_2]_n\cdot CO_2^-$$

Although oxidation of γ-branched-chain carboxylic acids by manganate gives good yields of γ-hydroxy-acids, that of α- or β-branched-chain acids results in extensive degradation of the molecule. It may be that in strongly alkaline solution zwitterions containing positive α- or β-carbon atoms readily eliminate a proton to form substituted acrylate ions, which would be susceptible to further attack, but that the removal of a hydride ion from the γ-carbon atom is facilitated by a simultaneous nucleophilic attack by the $\cdot CO_2^-$ group

on the γ-carbon atom to give a γ-lactone, which would then be hydrolysed to the salt of a stable hydroxy-acid:



In general, no evidence relating to the mechanism of oxidation by potassium permanganate in dilute alkaline solution ($MnO_4^- \longrightarrow MnO_2$) has been obtained. However, oxidation of optically active 4-methylhexanoic acid ($CO_2H = 1$) by this reagent yielded 4-hydroxy-4-methylhexanoic acid in small quantities, which possessed a rotatory power considerably smaller than that required for complete retention of optical activity. It is therefore possible that both types of reaction contributed to its formation. However, since the hydroxy-acid is unaffected by permanganate, and since the main part of the reaction consisted of a deep-seated oxidation, it is inferred that neither process contributes extensively to the main reaction.

The most cogent evidence in favour of the dual mechanisms resides in their complementary nature. Thus, it is expected that one mechanism would result in slight, and the other in extensive, racemisation: and two procedures have been found which exhibit these characteristics to the fullest extent.

Experimental

The preparation and characterisation of the racemic forms of the reactants and products, and the general procedures used for oxidation, are described in Part I (*loc. cit.*).

Preparation of Optically Active Branched-chain Carboxylic Acids.—(+)-α-Methylbutyric acid, prepared from a mixture of (−)-2-methylbutanol obtained from fusel oil (Le Couteur, Kenyon, and Rohan, *J. Appl. Chem.*, **1951**, **1**, 341) and (±)-2-methylbutanol, had b. p. 64°/2 mm., α_D^{20} +6·2° (*l*, 1·0) (optical purity 35·5%).

(−)-α-Phenylpropionic acid, partially resolved *via* its strychnine salt (Ott and Kramer, *Ber.*, 1935, **68**, 1651), had b. p. 96—97°/0·1 mm., α_D^{20} −9·07° (*l*, 0·5) (optical purity 17·5%).

(+)-γ-Phenylvaleric acid, prepared from (−)-α-phenylpropionic acid, α_D^{20} −9·07° (*l*, 0·5), had m. p. 16°, b. p. 98°/0·1 mm., α_D^{20} +1·84° (*l*, 0·5). [The optical purity calculated from the datum of Levene and Marker (*J. Biol. Chem.*, 1935, **110**, 329) is 17·5%, thus indicating that no racemisation occurred during the synthesis.]

(+)-4-Methylhexanoic acid, prepared from a mixture of (−)-2-methylbutanol (20%) and (±)-2-methylbutanol (80%) by conversion into the bromide, followed by a malonic ester synthesis, had b. p. 85°/2 mm., α_D^{20} +1·00° (*l*, 0·5) (optical purity 20%).

Preparation of Optically Active Hydroxy-carboxylic Acids.—(+)-α-Hydroxy-α-phenylpropionic acid, partially resolved *via* its quinine salt (Wren and Wright, *J.*, 1921, **119**, 798), had m. p. 112°, α_D^{20} +1·2° (*l*, 2; *c*, 5 in abs. EtOH).

(+)- and (−)-γ-Phenyl-γ-valerolactone were prepared from the brucine salt of the hydroxy-acid. Brucine (13·6 g.) was dissolved in an ice-cold solution of the (±)-hydroxy-acid (6·8 g.) in aqueous ethanol (75%), and some solvent removed *in vacuo*, since, when heated, the brucine salt tends to decompose into brucine and the lactone. After 7 days, the separated crystals (A) were removed [3·4 g.; m. p. 95° (decomp.)]. After removal of three further crops, obtained by evaporation under reduced pressure, the mother-liquors were partially evaporated and cooled to 0°, and the separated crystals (B) dissolved in water and acidified at 0° with dilute hydrochloric acid. The precipitated γ-hydroxy-γ-phenylvaleric acid, m. p. 120°, by repeated distillation with benzene, was converted into the γ-lactone, b. p. 99°/0·1 mm., α_D^{20} +27·9° (*l*, 0·5). Similarly, the final mother-liquors from (B) gave (+)-γ-phenyl-γ-valerolactone, α_D^{20} +27·8° (*l*, 0·5). Three recrystallisations of crop (A) from 75% alcohol gave (−)-γ-phenyl-γ-valerolactone, b. p. 103°/0·5 mm., α_D^{20} −27·95° (*l*, 0·5). Recrystallisation of the brucine salt did not alter the rotatory power of the lactone.

(−)-4-Hydroxy-4-methylhexanoic lactone was prepared from the (−)-1-phenylethylamine salt of the hydroxy-acid. Since no reaction occurred when 1-phenylethylamine was warmed with the lactone, and since the hydroxy-acid is very readily lactonised, the following procedure was adopted. A vigorously stirred, ice-cold mixture of ether and an aqueous solution of the sodium salt of the hydroxy-acid was acidified with dilute hydrochloric acid, and the ethereal solution of the liberated hydroxy-acid immediately added to an ethereal solution of an equivalent quantity of (−)-1-phenylethylamine, α_D^{20} −44·7° (*l*, 1·0). The precipitated salt, m. p. 112°, was recrystallised five times from acetone, the resulting needles, m. p. 122·5°, were dissolved in water, the solution was cooled and acidified, and the liberated hydroxy-acid extracted with ether. Repeated distillation with benzene to ensure complete lactonisation gave (−)-4-hydroxy-4-methylhexanoic lactone, b. p. 64°/0·5 mm., α_D^{20} −7·2° (*l*, 0·5). Two further crystallisations altered neither the m. p. of the salt nor the rotation of the lactone.

(+)-4-Hydroxy-4-methylhexanoic lactone was prepared from the brucine salt of the hydroxy-acid. This salt, prepared as described for the 1-phenylethylamine salt, had m. p. 91°, raised to 97·5° after ten recrystallisations from acetone. Decomposition of the resulting needles gave (+)-4-hydroxy-4-methylhexanoic lactone, b. p. 64°/0·1 mm., α_D^{20} +7·15° (*l*, 0·5). The m. p. of the salt and the rotation of the lactone were not altered by two further recrystallisations.

Oxidations.—(a) *With potassium permanganate in concentrated alkaline solution.* (+)-α-Methylbutyric acid, α_D^{20} +3·1° (*l*, 0·5), gave α-hydroxy-α-methylbutyric acid, b. p. 117°/11 mm., m. p. and mixed m. p. 71°, α_D^{20} 0·00° (Found: equiv., 117·1. Calc. for $C_5H_{10}O_3$: equiv., 118).

(−)-α-Phenylpropionic acid, α_D^{20} −9·07° (*l*, 0·5), gave α-hydroxy-α-phenylpropionic acid, m. p. and mixed m. p. 89°, α_D^{20} 0·00° (*l*, 0·5) (Found: equiv., 166·5. Calc. for $C_9H_{10}O_3$: equiv., 166).

(+)-4-Methylhexanoic acid, α_D^{20} +1·00° (*l*, 0·5), gave 4-hydroxy-4-methylhexanoic acid, which, after repeated distillation with benzene, gave the lactone, b. p. 65°/0·5 mm., α_D^{20} 0·00° (*l*, 0·5) (Found: equiv., 128·3. Calc. for $C_7H_{12}O_2$: equiv., 128).

(+)-γ-Phenylvaleric acid, α_D^{20} +1·84° (*l*, 0·5), gave γ-hydroxy-γ-phenylvaleric acid, b. p. 82°/0·1 mm., m. p. and mixed m. p. 104·5° (Found: equiv., 194. Calc. for $C_{11}H_{14}O_3$: equiv., 194), which, after repeated distillation with benzene, gave the (±)-lactone, b. p. 122°/1·0 mm., α_D^{20} 0·00° (*l*, 0·5).

(b) *With potassium manganate in dilute alkaline solution.* (+)-4-Methylhexanoic acid, α_D^{20} +2·00° (*l*, 1·0), gave (+)-4-hydroxy-4-methylhexanoic lactone, b. p. 85°/2 mm., α_D^{20} +1·43° (*l*, 1·0) (Found: equiv., 126·9).

(+)-γ-Phenylvaleric acid, α_D^{20} +1·84° (*l*, 0·5), gave γ-hydroxy-γ-phenylvaleric acid, b. p. 102°/1 mm., m. p. 107·5—111·5° (Found: equiv., 194·1. Calc. for $C_{11}H_{14}O_3$: equiv., 194), converted by repeated distillation with benzene into the (+)-lactone, b. p. 123°/1 mm., α_D^{20} +4·99° (*l*, 0·5).

(c) *With potassium permanganate in dilute alkaline solution.* (+)-4-Methylhexanoic acid, α_D^{20} +2·00° (*l*, 1·0), gave (+)-4-hydroxy-4-methylhexanoic lactone, b. p. 85°/2 mm., α_D^{20} +0·61° (*l*, 1·0) (Found: equiv., 127·6).

Thanks are expressed to Imperial Chemical Industries Limited for a grant.

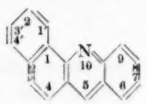
BATTERSEA POLYTECHNIC, LONDON, S.W.11.
[Present address (of M. C. R. S.), UNIVERSITY OF SOUTHAMPTON.] [*Received, June 24th,* 1953.]

720. *Carcinogenic Nitrogen Compounds. Part XV.* New Polysubstituted Angular Benzacridines and Benzophenarsazines.*

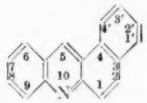
By Ng. Ph. Buu-Hoï, R. Royer, M. Hubert-Habart, and P. Mabille.

Polysubstituted angular benzacridines and benzophenarsazines bearing alkyl, fluorine, chlorine, methoxy-, and acetamido-groups, have been prepared. 2′ : 5′-Dimethyl-1 : 2-6 : 7-dibenzacridine has been synthesised from 1 : 6-dimethylnaphthalene, several derivatives of which are recorded.

In recent years, one of the most important tasks connected with research on chemical carcinogenesis has been the comparison of carcinogenic activities as determined experimentally in a given group of molecules, with the theoretical data derived from calculation of π-electron densities in these molecules by means of wave mechanics (Schmidt, *Naturwiss.*, 1941, **29**, 146; Lacassagne, Buu-Hoï, Rudali, and Lecocq, *Bull. Cancer*, 1946, **33**, 48; 1947, **34**, 22; Pullman, *ibid.*, p. 120; Buu-Hoï, Daudel, Lacassagne, Lecocq, Martin, and Rudali, *Compt. rend.*, 1947, **225**, 238; Daudel, Daudel, and Buu-Hoï, *Acta Un. int. Cancr.*, 1950, **7**, 91). The value of such a work depends on the number of compounds investigated within each series and, chemically, it necessitates the preparation of as many



(I)



(II)

derivatives as possible of a given parent hydrocarbon or heterocycle. In the relatively simple case of methyl derivatives of 1 : 2- (I) or 3 : 4-benzacridine (II), the number of theoretically possible isomers is :

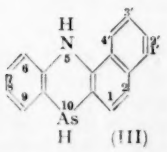
No. of Me groups	1	2	3	4	5	6	7	8	9	10	11
No. of isomers	11	55	165	330	462	462	330	165	55	11	1

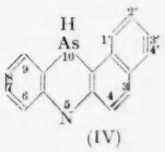
Hitherto, only one tetramethyl- (Buu-Hoï, *J.*, 1946, 792), seven trimethyl- (Senier and Austin, *J.*, 1907, **91**, 1233; Buu-Hoï, *loc. cit.*), seven dimethyl- (Senier and Compton, *J.*, 1907, **91**, 1927; 1909, **95**, 1623; Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 792; Buu-Hoï, *J.*, 1949, 670), and five monomethyl-3 : 4-benzacridines (Ullmann and Naef, *Ber.*, 1900, **33**, 905; Buu-Hoï, *loc. cit.*) had been prepared. We now report the preparation of a further one monomethyl, three dimethyl, two trimethyl, and four tetramethyl derivatives of 3 : 4-benzacridine; these, together with some 2′-methyl-3 : 4-benzacridines bearing in addition higher alkyl or methoxy-groups, are listed in Table 1. All were synthesised from 6-methyl- and 7-methyl-2-naphthol, either by the Ullmann–Fetvadjian reaction (*Ber.*, 1903, **36**, 1029), or in the case of the *meso*-substituted compounds, by the modified Bernthsen reaction (Buu-Hoï, *J.*, 1946, 792; 1949, 670); in view of the carcinogenic activity of 2-acetamidofluorene and other polycyclic amides, 7-acetamido-2′-methyl-3 : 4-benzacridine was prepared by condensing 6-methyl-2-naphthol with the reaction product of formaldehyde on *p*-aminoacetanilide (cf. Ullmann, *Chem. Zentr.*, 1901, II, 568); the free amine was obtained by hydrolysis. The pronounced carcinogenic activity of some fluorine-containing benzacridines described in a recent paper (Buu-Hoï and Jacquignon, *J.*, 1952, 4173) induced us to prepare several new *meso*-substituted 7-fluoro-1 : 2- and -3 : 4-benzacridines, listed in Table 1. Attempts to synthesise benzacridines bearing trifluoromethyl groups failed, as extensive decomposition occurred with *o*- and *p*-trifluoromethylaniline in the Knoevenagel reaction with naphthols and iodine (Knoevenagel, *J. pr. Chem.*, 1914, **89**, 17; Buu-Hoï, *J.*, 1952, 4346), and also under the conditions of the Ullmann–Fetvadjian reaction.

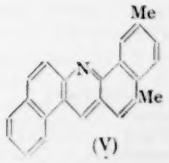
The mild tumour-provoking activity of certain 10-chloro-5 : 10-dihydrobenzophenarsazines (Lacassagne, Rudali, Buu-Hoï, and Royer, *Compt. rend. Soc. Biol.*, 1951, **145**, 1451) prompted

* Part XIV, Buu-Hoï and Xuong, *J.*, 1953, 386.

the preparation of a series of new polysubstituted derivatives of 5 : 10-dihydro-1 : 2- (III) and -3 : 4-benzophenarsazines (IV) by known methods (cf. Buu-Hoï and Royer, *J.*, 1951, 795). In the dibenzacridine group, 3 : 2′-dimethyl-1 : 2-6 : 7-dibenzacridine (V) was prepared by an Ullmann–Fetvadjian reaction on β-naphthol and 4 : 7-dimethyl-1-naphthylamine;


(III)


(IV)


(V)

the last compound was obtained from 4-acetyl-1 : 6-dimethylnaphthalene (cf. Feist, *J. pr. Chem.*, 1934, **139**, 261; Buu-Hoï and Cagniant, *Rev. sci.*, 1943, **81**, 173) by Beckmann rearrangement of its oxime; 4-ethyl- and 4-*iso*butyl-1 : 6-dimethylnaphthalene were also prepared.

The substances described here are under biological test in this Institute by Professor Lacassagne and Dr. Zajdela, and the results will be reported elsewhere.

Experimental

4 : 7-*Dimethyl*-1-*naphthylamine*.—4-Acetyl-1 : 6-dimethylnaphthalene (70 g.), prepared in the usual way from 1 : 6-dimethylnaphthalene (100 g.), acetyl chloride (55 g.), and aluminium chloride (100 g.) in carbon disulphide, was characterised by a Pfitzinger reaction with isatin, to give 2-(4 : 7-*dimethyl*-1-*naphthyl*)*cinchoninic acid*, which formed pale yellow needles, m. p. *ca.* 254—256° (decomp. from 238°), from acetic acid (Found: C, 80·3; H, 5·2. $C_{22}H_{17}O_2N$ requires C, 80·7; H, 5·1%). The oxime of the ketone (40 g.) was rearranged in ether with phosphorus pentachloride at 0°, and the crude amide obtained hydrolysed with concentrated hydrochloric acid. **4 : 7-*Dimethyl*-1-*naphthylamine*** (16 g.) obtained on basification was a pale yellow oil, b. p. 184—185°/15 mm. (Found: C, 84·0; H, 7·5. $C_{12}H_{13}N$ requires C, 84·2; H, 7·6%); its *benzoyl* derivative formed silky, sublimable needles, m. p. 225—226°, from methanol (Found: C, 82·6; H, 6·3. $C_{19}H_{17}ON$ requires C, 82·9; H, 6·2%), and its *toluene*-p-*sulphonyl* derivative formed needles, m. p. 218°, from ethanol (Found: C, 70·1; H, 6·0. $C_{19}H_{19}O_2NS$ requires C, 70·2; H, 5·8%).

3 : 2′-*Dimethyl*-1 : 2-6 : 7-*dibenzacridine* (V).—To a boiling mixture of the foregoing amine (4 g.) and β-naphthol (4 g.), heated at 250°, paraformaldehyde (0·8 g.) was added in small portions, and the product fractionated *in vacuo*; the portion of b. p. >300°/20 mm. was converted into a picrate (orange-yellow needles, from nitrobenzene) which gave on treatment with aqueous ammonia the free *base*, crystallising as pale yellow prisms, m. p. 175°, from ethanol (Found: C, 89·6; H, 5·4. $C_{23}H_{17}N$ requires C, 89·9; H, 5·5%).

4-*Ethyl*-1 : 6-*dimethylnaphthalene*.—4-Acetyl-1 : 6-dimethylnaphthalene (10 g.), reduced by 48 hours' refluxing with amalgamated zinc (50 g.), hydrochloric acid (250 c.c.) and toluene (10 c.c.), gave the *hydrocarbon* as a colourless oil (5 g.), b. p. 275—277°, $n_D^{19\cdot5}$ 1·5980 (Found: C, 91·1; H, 8·7. $C_{14}H_{16}$ requires C, 91·3; H, 8·7%).

4-iso*Butyl*-1 : 6-*dimethylnaphthalene*, a colourless oil, b. p. 290°, n_D^{21} 1·5725 (Found: C, 90·3; H, 9·5. $C_{16}H_{20}$ requires C, 90·6; H, 9·4%), was similarly obtained from **4-iso*butyryl*-1 : 6-*dimethylnaphthalene*** (12 g.), b. p. 195—198°/16 mm., n_D^{20} 1·5915, prepared from 1 : 6-dimethylnaphthalene (17 g.), *iso*butyryl chloride (15 g.), and aluminium chloride (15 g.) in carbon disulphide (Found: C, 85·2; H, 8·1. $C_{16}H_{18}O$ requires C, 85·0; H, 8·0%).

N-(2 : 4-*Dimethylphenyl*)-7-*methyl*-2-*naphthylamine*.—A mixture of 7-methyl-1-naphthol (10 g.; Shreve and Lux, *Ind. Eng. Chem.*, 1943, **35**, 306), 2 : 4-dimethylaniline (8·5 g.), and iodine (0·5 g.) was refluxed for 20 hr. and the product taken up in benzene, washed with aqueous alkali, and fractionated; the *diarylamine* (13 g.), b. p. 246—249°/16 mm., formed colourless prisms, m. p. 56°, from methanol (Found: N, 5·4. $C_{19}H_{19}N$ requires N, 5·4%); **N-(3 : 5-*dimethylphenyl*)-7-*methyl*-2-*naphthylamine***, similarly prepared from **3** : 5-dimethylaniline, formed needles, m. p. 112°, from ethanol (Found: N, 5·2%). **N-(2 : 4-*Dimethylphenyl*)-6-*methyl*-2-*naphthylamine*** (15 g.), prepared from 6-methyl-2-naphthol (10 g.; cf. Dziewoński, Schoeńowna, and Waldmann, *Ber.*, 1925, **58**, 1213), 2 : 4-dimethylaniline (8·5 g.), and iodine (0·5 g.), formed

colourless prisms, m. p. 75°, from ethanol (Found : N, 5·2%); N-(2 : 3-*dimethylphenyl*)-6-*methyl*-2-*naphthylamine* formed colourless prisms, m. p. 103°, from ethanol (Found : N, 5·3%); N-(5-*ethyl*-2-*methylphenyl*)-6-*methyl*-2-*naphthylamine* (16 g.) was a thick yellow oil, b. p. 248—250°/15 mm. (Found : N, 4·9. $C_{20}H_{21}N$ requires N, 5·1%).

TABLE 1.

(a) *Substituted* 1 : 2-*benzacridines.*

Substituent	M. p.	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
5-Ethyl-7-fluoro-	118°	$C_{19}H_{14}NF$	82·6	5·0	82·9	5·1
7-Fluoro-5-propyl	93	$C_{20}H_{16}NF$	83·1	5·5	83·0	5·3
7-Fluoro-5-pentyl- [a]	105	$C_{22}H_{20}NF$	83·1	6·5	83·3	6·3
5-Benzyl-7-fluoro- [b]	145	$C_{24}H_{16}NF$	85·2	4·8	85·5	4·7
(b) *Substituted* 3 : 4-*benzacridines.*						
2′-Methyl-	133°	$C_{18}H_{13}N$	88·8	5·5	88·9	5·3
9 : 2′-Dimethyl-	202	$C_{19}H_{15}N$	88·4	5·6	88·7	5·8
8 : 2′-Dimethyl-	170	$C_{19}H_{15}N$	88·5	5·8	88·7	5·8
7 : 2′-Dimethyl-	227	$C_{19}H_{15}N$	88·5	6·0	88·7	5·8
8 : 9 : 2′-Trimethyl-	190	$C_{20}H_{17}N$	88·3	6·3	88·6	6·3
7 : 9 : 2′-Trimethyl-	187	$C_{20}H_{17}N$	88·5	6·2	88·6	6·3
5 : 7 : 9 : 3′-Tetramethyl-	156	$C_{21}H_{19}N$	88·4	6·8	88·4	6·7
5 : 6 : 8 : 3′-Tetramethyl- [c]	—	$C_{21}H_{19}N$	88·3	6·7	88·4	6·7
5 : 7 : 9 : 2′-Tetramethyl-	168	$C_{21}H_{19}N$	88·2	6·6	88·4	6·7
5 : 8 : 9 : 2′-Tetramethyl-	147	$C_{21}H_{19}N$	88·2	6·9	88·4	6·7
5-Ethyl-8 : 2′-dimethyl-	184	$C_{21}H_{19}N$	88·0	6·8	88·4	6·7
8 : 2′-Dimethyl-5-propyl-	160	$C_{22}H_{21}N$	88·3	7·1	88·3	7·0
5-Ethyl-9 : 2′-dimethyl-	147	$C_{21}H_{19}N$	88·1	6·6	88·4	6·7
8-Chloro-5 : 9 : 2′-trimethyl-	140	$C_{20}H_{16}NCl$	78·8	5·1	78·6	5·2
6-Ethyl-5 : 9 : 2′-trimethyl-	146	$C_{22}H_{21}N$	88·1	7·2	88·3	7·0
5-Ethyl-7-fluoro-	169	$C_{19}H_{14}NF$	82·6	5·2	82·9	5·1
7-Fluoro-5-propyl-	140	$C_{20}H_{16}NF$	82·9	5·5	83·0	5·3
7-Fluoro-5-pentyl	119	$C_{22}H_{20}NF$	83·3	6·5	83·3	6·3
7-Fluoro-5-phenyl-	169	$C_{23}H_{14}NF$	85·5	4·5	85·4	4·3
7-Fluoro-5 : 2′-dimethyl-	158	$C_{19}H_{14}NF$	82·8	5·2	82·9	5·1
9-Methoxy-2′-methyl-	156	$C_{19}H_{15}ON$	83·6	5·3	83·5	5·5
7-Methoxy-2′-methyl-	220	$C_{19}H_{15}ON$	83·3	5·5	83·5	5·5
6 : 9-Dimethoxy-2′-methyl-	186	$C_{20}H_{17}O_2N$	79·3	5·4	79·2	5·6
7-Hydroxy-2′-methyl- [d]	>360	$C_{19}H_{13}ON$	83·4	5·1	83·4	5·0

(c) *Picrates of substituted* 3 : 4-*benzacridines.*

			N	N
2′-Methyl-	252°	$C_{24}H_{16}O_7N_4$	11·6	11·9
9 : 2′-Dimethyl-	256	$C_{25}H_{18}O_7N_4$	11·1	11·5
8 : 2′-Dimethyl-	280	$C_{25}H_{18}O_7N_4$	11·2	11·5
8 : 9 : 2′-Trimethyl-	262	$C_{26}H_{20}O_7N_4$	11·0	11·2
7 : 9 : 2′-Trimethyl-	309	$C_{26}H_{20}O_7N_4$	11·2	11·2
5 : 7 : 9 : 3′-Tetramethyl-	260	$C_{27}H_{22}O_7N_4$	11·0	10·9
5 : 6 : 8 : 3′-Tetramethyl-	250	$C_{27}H_{22}O_7N_4$	10·8	10·9
5 : 8 : 9 : 2′-Tetramethyl-	232	$C_{27}H_{22}O_7N_4$	10·8	10·9
5 : 7 : 9 : 2′-Tetramethyl-	238	$C_{27}H_{22}O_7N_4$	10·6	10·9
5-Ethyl-8 : 2′-dimethyl	260	$C_{27}H_{22}O_7N_4$	11·0	10·9
5-Ethyl-9 : 2′-dimethyl-	236	$C_{27}H_{22}O_7N_4$	11·1	10·9
5-Ethyl-7-fluoro-	225	$C_{25}H_{17}O_7N_4F$	10·8	11·1
7-Fluoro-5-*n*-propyl-	220	$C_{26}H_{19}O_7N_4F$	10·6	10·8
7-Fluoro-5-pentyl-	215	$C_{28}H_{23}O_7N_4F$	10·0	10·3
7-Fluoro-5 : 2′-dimethyl-	242	$C_{25}H_{17}O_7N_4F$	11·2	11·1
8-Chloro-5 : 9 : 2′-trimethyl-	228	$C_{26}H_{19}O_7N_4Cl$	10·3	10·5
6 : 9-Dimethoxy-2′-methyl-	243	$C_{26}H_{20}O_9N_4$	10·2	10·5

[a] Yellow picrate, m. p. 212°. [b] Yellow picrate, m. p. 229°. [c] The base did not crystallise, and was purified by vacuum-distillation. [d] Prepared from the corresponding methyl ether by 10 minutes' treatment with boiling pyridine hydrochloride, and decomposition with aqueous ammonia of the orange hydrochloride thus obtained; the product was recrystallised from xylene.

Condensation of Fluorinated Anilines with Naphthols.—*p*-Fluoroaniline (20 g.), 6-methyl-2-naphthol (23 g.), and iodine (0·3 g.) were refluxed for 5 hr.; the product, treated in the usual way, gave N-p-*fluorophenyl*-6-*methyl*-2-*naphthylamine* (22 g.), b. p. 200—204°/0·8 mm., forming colourless leaflets, m. p. 131°, from ethanol (Found : C, 81·5; H, 5·5. $C_{17}H_{14}NF$ requires C,

81·3; H, 5·6%); N-p-*fluorophenyl*-7-*methyl*-2-*naphthylamine*, b. p. 189—190°/0·5 mm., forme d colourless prisms, m. p. 127° (Found: C, 81·3; H, 5·6%).

7-*Acetamido*-2′-*methyl*-3 : 4-*benzacridine*.—A mixture of 6-methyl-2-naphthol (3 g.) with the condensation product (2·5 g.) of *p*-aminoacetanilide with formaldehyde was heated at 175—180° for 2 hr., and the product extracted with aqueous sodium hydroxide; the residue, washed with water and dried, formed grey crystals (3 g.), m. p. >350°, from xylene (Found: C, 79·9; H, 5·1. $C_{20}H_{16}ON_2$ requires C, 80·0; H, 5·3%); 7-*amino*-2′-*methyl*-3 : 4-*benzacridine*, obtained by hydrolysis of the foregoing *amide* with hydrochloric acid in ethanol and basification, formed grey prisms, m. p. 244° (Found: C, 83·6; H, 5·4. $C_{18}H_{14}N_2$ requires C, 83·7; H, 5·4%).

Benzacridine Syntheses (*see Table* 1).—(a) *By the modified Bernthsen method.* A mixture of equal weights of the appropriate diarylamine, acetic or propionic anhydride (or a higher acid), and freshly fused zinc chloride was heated at 170—180° for 24 hours; a large excess of 20% aqueous sodium hydroxide was added, and the product taken up in benzene and distilled *in vacuo*; purification was effected *via* the picrate, giving 25—50% yields of the benzacridine.

(b) *By the paraformaldehyde method.* To a boiling mixture of equal weights of the naphthol and the primary amine, paraformaldehyde (in slight excess) was added in small portions, and the product boiled for a few minutes before fractionation; the resulting benzacridine, purified *via* the picrate, was obtained in 15—40% yield.

TABLE 2.

(a) *Substituted* 5 : 10-*dihydro*-1 : 2-*benzophenarsazines*.

Substituent	M. p.	Decomp. begins at	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
10-Chloro-8-fluoro-	297°	270°	$C_{16}H_{10}NClFAs$	55·2	3·0	55·6	2·9
8-Fluoro-10-methyl-.....	120	—	$C_{17}H_{13}NFAs$	62·5	4·0	62·8	4·0
10-Chloro-8-fluoro-3′-methyl-...	285	270	$C_{17}H_{12}NClFAs$	56·5	3·2	56·8	3·3
10-Chloro-8-fluoro-2′-methyl-...	250	212	$C_{17}H_{12}NClFAs$	56·5	3·1	56·8	3·3
10-Chloro-6 : 8 : 2′-trimethyl-...	246	233	$C_{19}H_{17}NClAs$	61·5	4·5	61·7	4·6
10-Chloro-6 : 8 : 3′-trimethyl-...	276	260	$C_{19}H_{17}NClAs$	61·4	4·6	61·7	4·6

(b) *Substituted* 5 : 10-*dihydro*-3 : 4-*benzophenarsazines*.

10-Chloro-8-fluoro-	237	220	$C_{16}H_{10}NClFAs$	55·5	3·0	55·6	2·9
8-Fluoro-10-methyl-.....	107	—	$C_{17}H_{13}NFAs$	62·5	3·9	62·8	4·0

Phenarsazine Syntheses (*see Table* 2).—(a) 10-*Chloro*-5 : 10-*dihydrobenzophenarsazines*. A solution of the appropriate diarylamine and of the calculated amount of arsenic trichloride in the minimum quantity of *o*-dichlorobenzene, was refluxed for 6—8 hr.; the precipitate obtained on cooling was recrystallised from *o*-dichlorobenzene or xylene.

(b) 10-*Alkyl*-5 : 10-*dihydrobenzophenarsazines*. The appropriate 10-chloro-compound was added to an ethereal solution of alkylmagnesium halide, and the mixture refluxed for 10 min.; the ethereal layer obtained on treatment with aqueous ammonium chloride was dried and concentrated, to give the phenarsazine, which was recrystallised from ethanol or benzene.

This work is part of a cancer research scheme financially aided by the United States Public Health Service (Federal Security Agency); the authors express gratitude to the authorities concerned. They also thank Dr. G. C. Finger, Head of the Division of Fluorine Chemistry, State Geological Survey (Illinois, U.S.A.), for the generous gift of *o*- and *p*-trifluoromethylaniline, and Miss Patricia F. Boshell, M.A., for help with the work.

THE RADIUM INSTITUTE, UNIVERSITY OF PARIS. [*Received, July 1st,* 1953.]

721. *Studies of* Aspergillus niger. *Part II.** *Transglycosidation by* Aspergillus niger.

By S. A. Barker and T. R. Carrington.

Aspergillus niger (strain 152) (Yuill, *Chem. and Ind.*, 1952, 755) synthesises nigeran from a wide variety of carbohydrate substrates. It contains a transglucosidase responsible for the synthesis of *iso*maltose and panose from maltose, and transfructosidase(s) which utilise sucrose in the formation of trisaccharides.

Nigeran (originally named mycodextran), which was first isolated by Dox and Niedig (*J. Biol. Chem.*, 1914, **18**, 167; 1915, **20**, 83), has been shown recently (Barker, Bourne, and Stacey, *Chem. and Ind.*, 1952, 756; Part I*) to be a polyglycosan in which most, if not all, of the α-1 : 4- and α-1 : 3-linkages are arranged alternately. Before attempting to isolate the enzyme(s) responsible for the synthesis of nigeran, from *Aspergillus niger* " 152," it was decided to investigate the carbohydrate metabolism of this mould, and to determine the influence of trace ions present in the culture medium on the production of this novel glucosan.

Comparison of the growth of *A. niger* " 152 " in sucrose and Currie's medium (*J. Biol. Chem.*, 1917, **31**, 15), which contains Mg^{++}, Zn^{++}, and Fe^{++}, with that obtained in the absence of one of these ions, revealed that while the omission of Mg^{++} prevented growth, Fe^{++} deficiency produced a greater weight of mycelium and of nigeran than was obtained in the control medium. Although Zn^{++} deficiency did not prevent the formation of a mycelium, no nigeran was produced.

A study of the utilisation of a series of carbohydrate substrates and the storage of nigeran by *A. niger* " 152 " was followed by an examination of the residual culture medium (A), the soluble (C) and insoluble carbohydrates (B) present in a boiling-water extract of the mycelium after cooling, and the hydrolysable carbohydrates (D) retained by the extracted mycelium. Sodium acetate failed to support growth, and D-galactose, lactose, αα-trehalose, methyl α-D-glucopyranoside, and dipotassium α-D-glucose 1-phosphate gave only small mycelia in which nigeran could not be detected. D-Glucose, D-fructose, sorbitol, D-xylose, maltose, sucrose, starch, and inulin produced large mycelia which stored nigeran intracellularly, but only small amounts of the glucosan were obtained from mycelia grown on L-sorbose and D-mannitol (see Table 3, p. 3590).

Table 1. *Metabolism of certain substrates.*

Substrate	Other sugars produced having R_F values identical with those of :
Maltose	Glucose, *iso*maltose, panose, tetrasaccharide (trace : *iso*maltotriose, nigerose).
Starch	Glucose (trace : *iso*maltose).
Sucrose	Fructose, glucose, trisaccharides (trace : tetrasaccharide).
Inulin	Fructose (*inter al.*).
Fructose	Oligosaccharides? ($R_{Fructose}$ 0·63, 0·50, 0·41, 0·36).

No sugars other than the substrate were detected in (A) when the mould was grown on D-xylose, D-glucose, D-galactose, D-mannitol, sorbitol, L-sorbose, lactose, dipotassium α-D-glucose 1-phosphate, and methyl α-D-glucoside. After 10 days D-xylose and D-glucose had been completely utilised, but some sorbitol still remained. Substrates which gave rise to other sugars in the medium are listed in Table 1.

With all substrates which gave rise to nigeran, a component having an R_F value identical with that of glucose was found in (C). In all cases where growth was observed, the extracted mycelium, after hydrolysis, gave three components having mobilities identical with those of glucose, galactose, and fructose, suggesting the storage of these sugars as polysaccharides.

A closer investigation of the storage of nigeran by *A. niger* growing on glucose, sucrose, and maltose revealed that, whereas no nigeran could be detected after 3 days, it reached a maximum after about 5 days, further incubation only serving to increase the weight of

* Part I, *J.*, 1953, 3084.

mycelium obtained (Table 4, p. 3591). After the incubation of resting cells of *A. niger* (mycelium grown on sucrose, 3 days) with these same sugars, larger amounts of nigeran could be isolated than with a saline control. Similar but smaller amounts of nigeran were obtained by using the same resting cells after freeze-drying (Table 5, p. 3591).

With the exception of the production of the supposed oligosaccharides from fructose, the sugars formed from the substrates listed in Table 1 by propagating cells of *A. niger* were also produced by resting cells and by a cell-free extract of the mould. Since it was believed that the possible precursors of nigeran might be a trisaccharide or a disaccharide phosphate in which one of the glucosidic links (α-1 : 3 or α-1 : 4) was pre-formed, the synthesis of oligosaccharides from sucrose and maltose was investigated more closely.

The oligosaccharides produced from maltose by a cell-free extract of the mould were fractionated on a charcoal column (Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677) and characterised as crystalline sugars or their derivatives. The isolation of *iso*-maltose (6-*O*-α-D-glucopyranosyl-D-glucose), panose [*O*-α-D-glucopyranosyl-(1 ⟶ 6)-*O*-α-D-glucopyranosyl-(1 ⟶ 4)-α-D-glucopyranose], and glucose, and the detection of *iso*-maltotriose indicates the presence of an intracellular transglucosidase analogous to the extracellular enzymes produced by *A. niger* NRRL-337 (Pan, Andreasen, and Kolachov, *Science*, 1950, **112**, 115; *Arch. Biochem.*, 1951, **30**, 6; Pan, Nicholson, and Kolachov, *J. Amer. Chem. Soc.*, 1951, **73**, 2547) and by *A. oryzae* (Pazur and French, *J. Amer. Chem. Soc.*, 1951, **73**, 3536; *J. Biol. Chem.*, 1952, **196**, 265). The synthesis of a second disaccharide having a mobility equal to that of nigerose (3-*O*-α-D-glucosyl-D-glucose) is being further investigated.

Two trisaccharides, separated by the gradient elution method of Alm, Williams, and Tiselius (*Acta Chem. Scand.*, 1952, **6**, 826), and a tetrasaccharide were isolated from the products of the action of a cell-free extract of *A. niger* on sucrose. One trisaccharide, which constituted the major part of the trisaccharide fraction, was obtained crystalline. It was non-reducing, contained two D-fructose and one D-glucose residue, and had an R_F value identical with *O*-α-D-glucopyranosyl (1 ⟶ 2)-*O*-β-D-fructofuranosyl (1 ⟶ 2)-β-D-fructofuranoside, a trisaccharide produced from sucrose by using " Takadiastase " (Bacon and Bell, *J.*, in the press) and kindly supplied to us by Dr. J. S. D. Bacon. It had $[\alpha]_D^{16}$ +29·2° in H_2O, which was similar to the values between +30·5° and +32·6° reported by Bacon and Bell (*loc. cit.*) for their syrupy trisaccharide. The other trisaccharide was also non-reducing and contained two D-fructose and one D-glucose residue. Structural studies on these trisaccharides are in progress and will be reported later. Both of them, as well as the tetrasaccharide fraction, which contained three fructose and one glucose residue, presumably arose by transfer of fructosyl groups to sucrose, a phenomenon also found with extracts of other moulds (Wallenfels and Bernt, *Angew. Chem.*, 1952, **64**, 28; Bealing and Bacon, *Biochem. J.*, 1953, **53**, 277; Pazur, *J. Biol. Chem.*, 1952, **199**, 217).

Experimental

Effect of Trace Ions on the Synthesis of Nigeran.—A medium (250 c.c.) was prepared containing sucrose (37·5 g.), NH_4NO_3 (0·625 g.), KH_2PO_4 (0·25 g.), $MgSO_4,7H_2O$ (0·0625 g.), N-HCl (0·25 c.c.), $ZnSO_4,7H_2O$ (0·010 g.), and $FeSO_4,7H_2O$ (0·010 g.), together with three other similar media from which zinc sulphate, ferrous sulphate, and magnesium sulphate were severally omitted. The sulphate of the medium deficient in magnesium sulphate was supplied as ammonium sulphate (0·0625 g.). After inoculation with *Aspergillus niger* " 152," and incubation for 6 days at 30°, no growth was observed in the Mg^{++}-deficient medium. Nigeran (fraction 1) was isolated by washing each mycelium thoroughly with distilled water (6 × 100 c.c.) and extracting it with boiling water (2 × 100 c.c.) for 0·5 hr., successive extracts being filtered while hot, combined, and set aside at 0° for 18 hr. The nigeran precipitate was separated by centrifuging, washed with alcohol, and dried *in vacuo* over P_2O_5 at 60°. The extracted mycelium was dried at 100° and weighed (see Table 2). Further nigeran fractions were isolated by autoclaving the mycelium with water (100 c.c.) at 15 lb./sq. in. for 30 min. (fraction 2), and by extraction with cold N-sodium hydroxide (50 c.c.) for 24 hr. at room temperature, nigeran (fraction 3) separating on neutralisation of the filtered extract. Portions (20 mg.) of each fraction were submitted to partial hydrolysis by N-sulphuric acid at 90° for 2 hr. and the neutral-

ised hydrolysates analysed chromatographically as the free sugars and as their benzylamine derivatives (Bayly and Bourne, *Nature*, **1953**, **171**, 385) with a *n*-butanol (40%), ethanol (10%), water (49%), ammonia (1%) solvent mixture. Components having R_F values identical with those of glucose, maltose, and 3-*O*-α-D-glucosyl-D-glucose were detected. The optical rotation of each nigeran fraction was determined in N-sodium hydroxide.

TABLE 2. *Effect of trace ions on the synthesis of nigeran.*

	Control		Fe^{++}-deficient		Zn^{++}-deficient
Medium :	g.	$[\alpha]_D$	g.	$[\alpha]_D$	g.
Fr. 1	0·137	+225°	0·216	+243°	None
Fr. 2	0·049	+254	0·136	+250	None
Fr. 3	0·264	+234	0·450	+218	None
Mycelium	3·354	—	6·033	—	1·122

On repetition, the above experiment gave similar results. Extension of the time of incubation of the Zn^{++}-deficient medium from 6 to 12 days resulted in an increased yield of the extracted mycelium but this was not accompanied by the production of nigeran. The aqueous extract had only a negligible rotation but was stained blue with iodine.

Metabolism of Various Substrates by Propagating Cells of Aspergillus niger.—The carbohydrate substrate was dissolved in the mineral component of Currie's medium (10 g. in 100 c.c.), steam-sterilised, inoculated with aliquot volumes (1 c.c.) of a suspension of *A. niger* " 152 " and incubated at 30°. During incubation, spots of the medium were submitted to paper chromatography as described above, the papers being sprayed with aniline hydrogen phthalate (Partridge, *Nature*, 1949, **164**, 443) for reducing sugars, naphtharesorcinol (Partridge, *Biochem. J.*, 1948, **42**, 238) for keto-sugars, and ammoniacal silver nitrate (Hough, *Nature*, 1950, **165**, 400) for non-reducing sugars and sugar-alcohols. After 10 days, the residual culture medium (A) was decanted from the mycelial felts, the mycelia were washed and extracted with boiling water (100 c.c. × 1; 50 c.c. × 3), and the nigeran (B) was obtained as described above. The supernatant extract (C) was concentrated to a small volume (10 c.c.) and analysed chromatographically. The residual mycelium (D) was washed with alcohol and ether and dried. No growth was observed with sodium acetate as the substrate.

TABLE 3. *Production of nigeran from various substrates.*

	Yield (as % of substrate)			Sugars in hydrolysate of *B*	Infra-red analysis of *B*,* 700—960 cm.$^{-1}$
Substrate	*B* (Nigeran)	*D*	$[\alpha]_D$ of *B*		
D-Xylose	0·39	13·67	+231°	Glucose	Nigeran
D-Glucose	2·77	23·50	+243	Glucose	Nigeran
D-Galactose	None	0·38	—	—	—
D-Fructose	1·37	21·80	+209	Glucose	Nigeran
L-Sorbose	0·01	17·70	—	Glucose	Nigeran
D-Mannitol	0·01	8·33	—	Glucose	Nigeran
D-Sorbitol	1·04	12·46	+226	Glucose	Nigeran
α-D-Glucose 1-phosphate	None	0·20	—	—	—
Methyl α-D-glucoside	None	0·20	—	—	—
Maltose	1·80	19·04	+253	Glucose	Nigeran
Sucrose	1·60	19·44	+247	Glucose	Nigeran
Lactose	None	0·89	—	—	—
αα-Trehalose	None	0·20	—	—	—
Melezitose	None	6·61	—	—	—
Starch	0·82	25·30	+201	Glucose (fructose)	Nigeran
Inulin	1·50	18·22	+202	Glucose (fructose)	Nigeran

* Barker, Bourne, Stacey, and Whiffen, *Chem. and Ind.*, 1953, 196.

Rates of Storage of Nigeran by Aspergillus niger.—Digests containing severally glucose, maltose, and sucrose (15 g.), together with mineral medium (150 c.c.), were each prepared in triplicate, sterilised, inoculated with aliquots (5 c.c.) of a suspension of *A. niger* in sterile distilled water, and incubated at 30°. After 3, 5, and 7 days a culture of each of the three substrates was removed for analysis. Spots of the medium were analysed chromatographically and nigeran was extracted as above from each mycelium with boiling water (5 × 50 c.c.). The extracted cell residues were dried in the usual manner.

Metabolism of Resting Cells of Aspergillus niger *with Various Substrates.*—Freeze-dried washed cells (1·009 g.) of *A. niger*, which had been previously grown on sucrose, were suspended

in water (20 c.c.) and portions (1 c.c.) added to each of a number of 2·5% carbohydrate solutions (2 c.c.) in centrifuge tubes; the mixtures were shaken and incubated at 30°. Spots of the supernatant liquid obtained after centrifuging were removed after 3 and 24 hr. and the

TABLE 4. *Storage of nigeran by* A. niger.

Substrate	Days of incubation	Yield of nigeran (as % of substrate)	$[\alpha]_D$ of nigeran	Yield of extracted cells (as % of substrate)	Sugars detected in medium: Main	Trace
Glucose ...	3	None	—	6·1	Glucose	—
,, ...	5	1·86	+254°	15·9	—	Glucose
,, ...	7	1·78	+248	23·4	—	—
Sucrose ...	3	None	—	6·0	Sucrose, glucose, fructose	Trisaccharide
,, ...	5	1·97	+249	15·9	Glucose, fructose	Sucrose
,, ...	7	1·62	+259	26·4	—	—
Maltose ...	3	None	—	4·7	Maltose, glucose	Panose, *iso*maltose
,, ...	5	1·44	+247	14·6	Glucose	Maltose, *iso*maltose, panose
,, ...	7	1·46	+252	18·2	—	*iso*Maltose, glucose

cells resuspended. The spots were analysed on paper chromatograms with the solvents and sprays enumerated above.

Effect of Freeze-drying on the Synthesis of Nigeran by Resting Cells.—A washed three-day mycelium of *A. niger*, grown on sucrose, was shredded in a Waring Blender and again washed free from cell debris with water. The moist cells were divided, one-half was freeze-dried and stored at 0°, and the other added in equal amounts (4·0 g.) to sterile solutions of glucose, maltose, and sucrose (7·5 g.) in water (50 c.c.) and to a control solution of N-sodium chloride (50 c.c.). A comparative experiment was carried out with freeze-dried cells in equivalent amounts (1·23 g.). After 7 days' incubation, the nigeran was obtained from each digest by four boiling-water extractions in the usual manner. The extracted cell residues were dried and weighed. A control extraction of fresh resting cells (4 g.) gave 0·834 g. of extracted cell residue and 0·026 g. of nigeran (see Table 5).

TABLE 5. *Effect of freeze-drying on resting cells.*

	Fresh-resting cells			Freeze-dried resting cells		
Substrate	Nigeran (g.)	$[\alpha]_D$ of nigeran	Extracted cell residue (g.)	Nigeran (g.)	$[\alpha]_D$ of nigeran	Extracted cell residue (g.)
Glucose	0·058	+260°	1·283	0·048	+239°	0·918
Maltose	0·091	+279	1·186	0·067	+231	0·590
Sucrose	0·072	+278	1·070	0·038	+232	0·335
Saline	0·030	+238	0·464	0·027	+267	0·329

Preparation of a Cell-free Intracellular Enzyme Extract.—A suspension of freeze-dried cells of *A. niger* (1 g.) in water or buffer was shaken at 0° with glass beads for 20 min. in a Mickle Tissue Disintegrator, and the cell debris washed out with water (20 c.c.), shaken for 1 hr., and centrifuged at 5000 r.p.m. to eliminate cell debris. A spot of the extract was stained with carbofuchsin to confirm the absence of unbroken cells.

Effect of a Cell-free Extract of A. Niger *on Various Substrates.*—Digests containing the cell-free enzyme extract (1 c.c.) with each of a series of 2·5% carbohydrate substrate solutions (2 c.c.) were incubated at 37° and spots of the solutions analysed chromatographically in the manner previously described.

Isolation of the Oligosaccharides synthesised from Maltose by a Cell-free Extract.—A cell-free 0·2M-citrate extract (pH 6·2; 20 c.c.) of freeze-dried *A. niger* (0·786 g.) was added to a maltose solution (6·985 g. in 200 c.c. of water), layered with toluene, and incubated at 30—35°; the production of oligosaccharides was followed on a paper chromatogram. After 8 days, enzyme action was arrested by heating at 100° for 15 min., the absence of polysaccharide in the culture filtrate confirmed by addition of methanol (3 vol.), and the solution concentrated to dryness *in vacuo*. The residue was extracted with dry methanol (200 c.c.) under reflux; the extract was cooled, filtered from insoluble citrate, and concentrated *in vacuo*. The residue was dissolved in water (100 c.c.) and fractionated on a charcoal column with increasing concentrations of aqueous ethanol (Whistler and Durso, *loc. cit.*). After paper-chromatographic analysis, similar

fractions were combined, concentrated, purified by methanol extraction, and freeze-dried. The yields and contents of these fractions are shown in Table 6.

TABLE 6. *Oligosaccharide fractions.*

Fraction	Chromatographic analysis	Yield (g.)
I	Glucose	0·651
II	*iso*Maltose	0·789
III	Maltose	0·959
IV	Panose	0·923
V	Multicomponent mixtures	0·379

Characterisation of the Oligosaccharide Fractions.—Crystallised from absolute methanol, fraction I gave α-D-glucose (0·476 g.), m. p. and mixed m. p. 141·5—143·5°, $[\alpha]_D^{17}$ +52° (*c*, 1·039 in H_2O; equil.) (Found: C, 40·0; H, 6·8. Calc. for $C_6H_{12}O_6$: C, 40·0; H, 6·7%). The glucose was further characterised as its β-penta-acetate, m. p. and mixed m. p. 130—132° (Found: C, 49·1; H, 5·6. Calc. for $C_{16}H_{22}O_{11}$: C, 49·15; H, 5·6%).

Fraction II was chromatographically pure *iso*maltose, having $[\alpha]_D^{17}$ +122·9° (*c*, 0·154 in H_2O) when corrected for ash (4·88%), and giving only glucose on hydrolysis with 2N-sulphuric acid. The *iso*maltose (0·0684 g.) was acetylated at 30—35° for 48 hr. with freshly distilled acetic anhydride (0·7 c.c.) and pyridine (3·5 c.c.). The resulting solution was heated at 100° for 30 min., cooled, and poured into ice-water. The crude acetate was extracted with chloroform and recrystallised from absolute ethanol. The β-*iso*maltose octa-acetate (0·0286 g.) obtained had m. p. 142·5—144·5°, alone or in admixture with an authentic specimen kindly supplied by Prof. M. L. Wolfrom (Found: C, 49·9; H, 5·7. Calc. for $C_{28}H_{38}O_{19}$: C, 49·6; H, 5·65%).

Fraction IV was heated under reflux in hot aqueous methanol (H_2O 2 c.c.; methanol 4 c.c.) for 8 hr., cooled, seeded, and allowed to crystallize according to the method of Pan, Nicholson, and Kolachov (*loc. cit.*). The panose obtained (0·367 g.) had m. p. 224—225·5° (decomp.), undepressed on admixture with an authentic specimen kindly supplied by Dr. Pan, and showed $[\alpha]_D^{17}$ +154° ⟶ +152·3° (36 hr.; equil.) (*c*, 0·559 in H_2O) (Found: C, 42·8; H, 6·3. Calc. for $C_{18}H_{32}O_{16}$: C, 42·9; H, 6·4%). Its infra-red absorption spectrum in the region 11—14 μ was identical with that of the authentic specimen. Hydrolysis with 1·5N-sulphuric acid for 5 hr. at 100° resulted in a 97·3% conversion into glucose. Partial hydrolysis with 0·34N-H_2SO_4 at 90° for 1 hr. gave glucose, maltose, *iso*maltose, and unchanged panose (identified by paper chromatography). Partial hydrolysis of the aldonic acid formed by oxidation of the trisaccharide (0·005 g.) in water (5 c.c.) with 0·1N-iodine (1 c.c.) and 0·2M-bicarbonate buffer (2 c.c.; pH 10·6) at room temperature for 2·5 hr. gave glucose and *iso*maltose as the only unoxidised sugars.

Crystalline material (0·077 g.), obtained from the mother-liquors after the crystallization of panose, had m. p. 213—214° (decomp.). Chromatographic analysis (benzylamine technique: Bayly and Bourne, *loc. cit.*) showed the presence of panose together with small amounts of a second trisaccharide having R_F identical with that of *iso*maltotriose.

Among the mixtures constituting fraction V, some contained a second disaccharide having R_F identical with that of 3-*O*-α-D-glucosyl-D-glucose and a tetrasaccharide.

Isolation of the Oligosaccharides synthesised from Sucrose by a Cell-free Extract.—A freeze-dried cell-free extract of *A. niger* (1·2 g.) was incubated with a sucrose solution (65 g. in 400 c.c. of water) at 37° and the production of oligosaccharides followed on a paper chromatogram. After 52 hr. the enzyme action was arrested and a preliminary fractionation effected on a charcoal column as described above. Fractions containing mainly glucose, fructose, or sucrose were discarded, and the higher oligosaccharides eluted by aqueous ethanol were obtained in two fractions. One fraction (1·088 g.) contained chromatographically pure trisaccharide I, while the other (1·671 g.), after gradient elution with 0—12% aqueous ethanol on a charcoal column (Alm, Williams, and Tiselius, *loc. cit.*), gave trisaccharide II (0·040 g.), further trisaccharide I (0·359 g.), and a tetrasaccharide fraction (0·082 g.), together with traces of higher oligosaccharides.

Examination of Oligosaccharide Fractions.—Trisaccharide I (1·088 g.) was dissolved in dry methanol, filtered, concentrated, precipitated by addition of dry ethanol, redissolved, and set aside to crystallize. Several crops of crystalline trisaccharide I (in all 0·587 g.) were obtained, having m. p. 82—88° (indef. with decomp.), $[\alpha]_D^{16}$ +29·2° (*c*, 0·584 in H_2O) unchanged after 18 hr. Its R_F value on a paper chromatogram was identical with that of *O*-α-D-glucopyranosyl (1 ⟶ 2)-*O*-β-D-fructofuranosyl (1 ⟶ 2)-β-D-fructofuranoside, the syrupy trisaccharide isolated by Bacon and Bell (*loc. cit.*). It was non-reducing to Shaffer–Hartmann solution (*J. Biol. Chem.*,

1921, **45**, 349). On partial hydrolysis it gave components having R_F values identical with those of sucrose, glucose, and fructose, and after complete hydrolysis the ratio of fructose to glucose was 2·1 : 1 (Van der Plank, *Biochem. J.*, 1936, **30**, 460).

Trisaccharide II showed $[\alpha]_D^{18}$ +33·6° (*c*, 0·417 in H_2O), was non-reducing, and after complete hydrolysis the ratio of fructose to glucose present was 1·8 : 1.

The tetrasaccharide fraction showed $[\alpha]_D^{18}$ +16·7° (*c*, 0·042 in H_2O), was non-reducing, and after complete hydrolysis the ratio of fructose to glucose present was 2·7 : 1.

The authors are indebted to Dr. J. S. D. Bacon for the sample of his trisaccharide. They also express their gratitude to Professor M. Stacey, F.R.S., and Dr. E. J. Bourne for their helpful discussion and interest, and to the British Rayon Research Association and British Celanese Ltd. for personal financial assistance.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15. [*Received, July 10th*, 1953.]

---

722. *Heterocyclic Imines and Amines. Part II.* Derivatives of* iso*Indoline and* iso*Indolenine.*

By P. F. CLARK, J. A. ELVIDGE, and R. P. LINSTEAD.

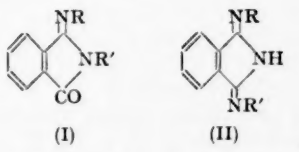
The reaction between imino-derivatives of *iso*indoline and bases has been further studied. 3-Imino-1-oxo*iso*indoline (I; R = R′ = H) gives the 2-unit products (I; R ≠ H, R′ = H) when condensed with 2-aminonaphthalene and 3-aminopyridine. Two mols. of (I; R = R′ = H) condense with 2 : 7-diaminonaphthalene, 3 : 5-diaminopyridine, and 2 : 4-diaminopyrimidine yielding the 3-unit products (III).

1 : 3-Di-imino*iso*indoline (II; R = R′ = H) gives the 3-unit compounds (II; R = R′ ≠ H) when condensed with an excess of the bases, aniline, 2-naphthylamine, *n*-butylamine, 3-aminopyridine, and aminopyrazine. The dipyrazinylimino-product formed a dimethiodide.

Di-imino*iso*indoline also reacts stepwise, forming with 1 mol. of base the monosubstituted imines (II; R′ = H), which are alternatively prepared by the catalysed addition of amines to phthalonitrile. The monosubstituted di-imines (II; R′ = H, R ≠ H) are hydrolysed to the oxo-compounds (I; R′ = H), and condense easily with a further mol. of primary base. Secondary bases also condense, yielding 3-amino-1-imino*iso*indolenine derivatives.

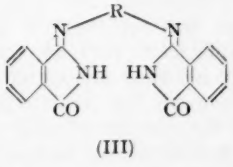
Quantitative degradations have been made, structures are discussed, and light-absorption data given.

THE *iso*indoline-imines (I and II; R = R′ = H) condense readily with primary amines, with elimination of ammonia, to give substituted imino-derivatives (I; R′ = H, R ≠ H) and (II) (Part I *). Further examples of these condensations are now described and the structures of the products discussed.

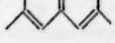


(I)

(II)



(III)

a; R = 

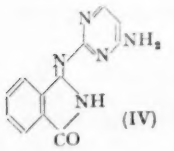
b; R =

c; R =

With 2-aminonaphthalene and 3-aminopyridine, the oxo-imine (I; R = R′ = H) yielded the 2-unit products (I; R = 2-$C_{10}H_7$, R′ = H) and (I; R = 3-C_5H_4N, R′ = H), as expected.

* Part I, *J.*, 1952, 5000. The original title of the series " Heterocyclic Imines " has been expanded in the light of new knowledge on the structure of the group of compounds under investigation.

Further, analogously to *m*-phenylenediamine (Part I), 2 : 7-diaminonaphthalene condensed in boiling alcohol with 2 mols of the oxo-imine (I; R = R′ = H), forming the 3-unit product (III*a*). 3 : 5-Diaminopyridine likewise gave the product (III*b*), and it showed no obvious tendency to react stepwise as does 2 : 6-diaminopyridine (Part I).



(IV)

The less reactive 2 : 4-diaminopyrimidine was best condensed with (I; R = R′ = H) in boiling nitrobenzene, (III*c*) being formed. Under milder conditions a mixture was obtained, mainly of 2-unit products, one of which was isolated. This may have the orientation (IV) because benzoylation and oxidation (cf. Wolf, Anderson, Kaczka, Harris, Arth, Southwick, Mozingo, and Folkers, *J. Amer. Chem. Soc.*, 1947, **69**, 2753) failed to yield benzoylguanidine.

The formation of the bis-condensation products (III), by interaction of the foregoing (sterically favourable) diamines with the oxo-imine (I; R = R′ = H), indicated that macrocycles should result from their condensation with the di-imine (II; R = R′ = H). A macrocycle has been prepared in this way from 2 : 6-diaminopyridine (Elvidge and Linstead, *J.*, 1952, 5008). However, we studied first the condensations of relevant monoamines with di-imino*iso*indoline. This gave the expected linear products, the structures of which were established. Their light absorptions are given in the Table (p. 3596). The preparation of further macrocycles will be described later.

With an excess of aniline in boiling alcohol, 1 : 3-di-imino*iso*indoline (II; R = R′ = H) gave 1 : 3-diphenylimino*iso*indoline (II; R = R′ = Ph). This base was also prepared from its deep-yellow hydrochloride, described in Part I. Mr. N. Haddock of Imperial Chemical Industries Limited, Dyestuffs Division, had reported to us the formation of the monosubstitution product, 1-imino-3-phenylimino*iso*indoline (II; R = Ph, R′ = H) (cf. Bayer Farbenfabr., Indian P. 43,679), and we confirmed its formation from the di-imine with 1 mol. of aniline, and as an intermediate in the reaction with an excess of aniline.

The monophenyl product (II; R = Ph, R′ = H) was also obtained from the sodium methoxide-catalysed interaction of phthalonitrile and aniline in methanol, a process which appears general (Bayer Farbenfabr., *loc. cit.*) and which with *n*-butylamine afforded 3-butylimino-1-imino*iso*indoline (II; R = Bu^n, R′ = H).

The unsubstituted imino-group of these products is reactive. Thus with an excess of butylamine, (II; R = Bu^n, R′ = H) readily gave 1 : 3-dibutylimino*iso*indoline (II; R = R′ = Bu^n), also obtained directly from di-imino*iso*indoline and an excess of butylamine. The monophenylimine (II; R = Ph, R′ = H) with aniline yielded the 1 : 3-diphenylimino-compound, whilst brief treatment with hydrochloric acid hydrolysed it to the oxo-compound (I; R = Ph, R′ = H); boiling hydrochloric acid rapidly gave 1 mol. each of phthalimide and aniline. Under the last conditions, the 1 : 3-diphenylimino-compound (II; R = R′ = Ph) was split to 1 mol. of phthalimide and 2 mols. of aniline (isolated as phenylazo-2-naphthol).

These hydrolyses and reactions supported the *iso*indoline structures. We made some additional experiments with 1-oxo-3-phenylimino*iso*indoline (I; R = Ph, R′ = H), however, because of apparent discrepancies with the literature.

Thus a compound with the same superficial properties as our oxo-phenylimine (I; R = Ph, R′ = H), which Porter, Robinson, and Wyler (*J.*, 1941, 620) prepared from monothiophthalimide and aniline, was reported by them to yield *N*-phenylphthalimide on hydrolysis. Reissert and Holle (*Ber.*, 1911, **44**, 3027) gave the 2-phenyl structure (I; R = H, R′ = Ph) to a seemingly identical compound from fusion of thiophthalanil and urea. They gave its methyl derivative the 3-methylimino-2-phenyl structure (I; R = Me, R′ = Ph). We found that the oxo-phenylimine yielded phthalimide almost immediately with hot aqueous acid, which confirms our 3-phenylimino-structure (I; R = Ph, R′ = H). After prolonged boiling and partial evaporation of the solution, *N*-phenylphthalimide was indeed obtained, but this is clearly a secondary product, without direct significance for the structure of the phenylimine. We regard Reissert and Holle's 2-phenyl structure as incorrect : evidently the urea fusion involves a molecular rearrangement. Additional evidence came from an examination of the methyl derivative.

We prepared this methyl derivative, which tallied with Reissert and Holle's description,

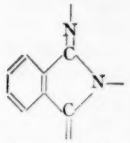
from the 1-oxo-3-phenyliminoisoindoline with methyl sulphate and alkali. That it had the 2-methyl-3-phenylimino-structure (I; R = Ph, R′ = Me), and not Reissert's proposed structure, was confirmed by its rapid hydrolysis with acid to *N*-methylphthalimide, and by an alternative preparation. 3-Imino-1-oxoisoindoline (I; R = R′ = H) was warmed with methyl sulphate yielding a methyl hydrogen sulphate; this was shown to be the salt of the 3-imino-2-methyl derivative (I; R = H, R′ = Me) by its hydrolysis with boiling water to *N*-methylphthalimide. Reaction of the imine salt with aniline produced the 2-methyl-1-oxo-3-phenyliminoisoindoline already encountered.

We next showed that the stepwise reaction of 1 : 3-di-iminoisoindoline with aniline was paralleled by its behaviour with some other amines. From the di-imine, with β-naphthylamine, either the mononaphthylimino-product (II; R = β-$C_{10}H_7$, R′ = H) or 1 : 3-dinaphthyliminoisoindoline (II; R = R′ = β-$C_{10}H_7$) was formed depending on the conditions. Conversion of the former into the latter product occurred readily with an excess of β-naphthylamine in boiling alcohol. With warm concentrated hydrochloric acid, the monoimine (II; R = β-$C_{10}H_7$, R′ = H) was hydrolysed to the oxo-compound (I; R = β-$C_{10}H_7$, R′ = H), identical with that from 3-imino-1-oxoisoindoline (I; R = R′ = H) and β-naphthylamine. Much more vigorous hydrolysis of the monoimine (II; R = β-$C_{10}H_7$, R′ = H) was required to effect further degradation: a boiling mixture of concentrated hydrochloric acid and ethanol produced phthalic acid and β-naphthylamine in high yields and equivalent proportions. Surprisingly, the dinaphthyliminoisoindoline (II; R = R′ = β-$C_{10}H_7$) resisted these conditions, but was split to phthalic acid and 2 mols. of β-naphthylamine by a boiling concentrated hydrochloric–acetic acid mixture.

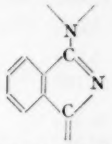
Thus the 1 : 3-disubstituted imino-compounds (II) derived from aniline and β-naphthylamine (and from 2-aminopyridine, Part I) are hydrolysed with very different ease. This no doubt depends on solubility differences, as well as on the stability of the C:N link, which are both influenced by the substituents.

The condensation in boiling ethanol of 1 : 3-di-iminoisoindoline with 3-aminopyridine, even in excess, gave only the monosubstituted imine (II; R = 3-C_5H_4N, R′ = H). The 1 : 3-di-3′-pyridyliminoisoindoline (II; R = R′ = 3-C_5H_4N) was produced by heating the reactants in butanol. Aminopyrazine, on the other hand, gave the 1 : 3-dipyrazinylimino-compound (II; R = R′ = $C_4H_3N_2$) directly under mild conditions. This product formed a dimethiodide, like the corresponding pyridine analogue (Part I).

Fine Structure.—The iminoisoindoline structures for the compounds described above and in the earlier paper are consistent with the reactions so far studied. The compound



A, Iminoisoindoline type.



B, Aminoisoindolenine type.

(I; R = Ph, R′ = Me) has a fixed iminoisoindoline structure (type *A*), but presumably the other (incompletely substituted) derivatives are capable of tautomerism and may exist in the amino-*iso*indolenine form (type *B*). Indeed, the amino-form *B* might be expected to predominate over imino-forms (see Angyal and Angyal, *J.*, 1952, 1461). The cation of these bases will exist as a resonance-stabilised hybrid.

To gather information on the fine structure of the bases we prepared several fully substituted derivatives of the second tautomeric form *B* by condensing secondary amines with the imines (I; R = R′ = H), (II; R = R′ = H), and (II; R = H, R′ = Ph).

The oxo-imine (I; R = R′ = H) with (undried) morpholine yielded the phthalic amide morpholide (V), also prepared by fission of phthalimide with aqueous morpholine. However, with redistilled (drier) morpholine, the oxo-imine gave the required substitution product, $C_{12}H_{12}O_2N_2$, which necessarily has the 3-morpholino-1-oxoisoindolenine structure (VI). This absorbs ultra-violet light to much longer wave-lengths than *o*-cyanobenzamide

or the phthalic amide derivative (V) which lack the fused pyrrolic ring (see Table). The compound (VI) was also formed from 1 : 3-di-imino*iso*indoline (II; R = R′ = H) under these conditions, the expected morpholino-imine evidently having been hydrolysed

Light-absorption data.

(For ethanol solutions, except where otherwise indicated.)

Compound	$\lambda_{max.}$ (Å)	ε
o-Cyanobenzamide	2260	13,400
(V)	2270	8,600
Phthalimide	2260 *	17,600
	2360	10,000
(I; R = R′ = H)	2270	11,500
	2370	10,500
	2510	6,570
	2920	3,500
(I; R = Ph, R′ = Me)	2470 *	17,900
	2510	18,900
	2810	3,800
	2910	
	3020	
(VI)	2510	7,350
	2670	9,900
	2800	8,400
	3070	3,700
	3270	3,200
	3430	
(I; R = 2-$C_{10}H_7$, R′ = H)	2420	10,900
	2510	
	2800	11,700
	3300	5,700
	3520	
(I; R = 3-C_5H_4N, R′ = H)	2280	16,500
	2420	
	2510	17,800
	2560	
	2800	8,000
	2900	6,900
	3020	
	3240	4,700
(III*a*) in dioxan	2260	69,000
	2510	59,500
	2560	73,500
	2600	59,500
	2800	22,800
	2900	21,200
	3020	
	3300 *	10,800
	3460	14,100
	3580	10,800
(III*b*) in H·CO·NMe_2	2800	11,400
	3040	14,700
	3250	8,000
	3480	7,000
(III*c*) in H·CO·NMe_2	2800	17,100
	3020	14,800
	3170	13,700
	3380	11,800
(II; R = R′ = H)	2510	12,500
	2560	
	3030	4,600
(II; R = Ph, R′ = H)	2510	14,800
	2570	
	2650	16,300
	2800	12,400
	3040	9,300
	3240	
	3300	
	3600	7,300
(II; R = R′ = Ph)	2510	12,200
	2570	
	2640	
	3030	8,900
	3280	
	3480	7,700
	3650	6,500
(II; R = 2-$C_{10}H_7$, R′ = H)	2300	55,500
	2510	16,800
	2590	21,700
	2660	
	3430	7,600
	3670	8,400
(II; R = R′ = 2-$C_{10}H_7$)	2270	63,500
	2340	
	3260	9,100
	3600	10,700
(II; R = Bu, R′ = H)	2510	12,000
	2580	13,600
	2640	
	2800 *	7,000
	3040	5,400
	3150 *	4,600
(II; R = R′ = Bu)	2510	8,000
	2660	11,000
	2780	8,000
	3040	6,000
	3150	
(II; R = 3-C_5H_4N, R′ = H)	2680	15,700
	2800	11,300
	3450	8,900
	3600 *	7,100
(II; R = R′ = 3-C_5H_4N)	2350	29,900
	2570	14,300
	2660	12,500
	2800	
	2900	
	3040	
	3150	
	3530	10,700
(II; R = R′ = 2-$C_4H_3N_2$)	2350	19,500
	2650	16,200
	2800	18,000
	2940	
	3050	
	3240	
	3480	12,900
	3860	19,500
	4100	9,600
(VII; R = O)	2270	29,100
	2360	25,600
	2650	9,600
	2800	
	2900	
	3750	11,300
(VII; R = CH_2)	2640	13,400
	2800	11,000
	3600 *	13,000
	3790	14,500
	3880 *	13,000
(VIII)	2580	11,200
	2680	12,400
	2810	
	2900	
	3680	14,600

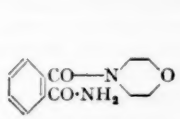
* Inflexion.

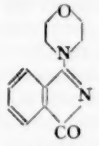
to (VI) by traces of moisture. With aqueous acid the *iso*indolenine (VI) yielded phthalimide and morpholine, the hydrolysis proceeding as readily as that of the true *iso*indoline (I; R = Ph, R′ = Me).

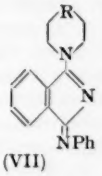
The monophenylimine (II; R = Ph, R′ = H) condensed with morpholine, piperidine, and *N*-methylaniline in boiling alcohol to yield the 3-amino-1-imino*iso*indolenines (VII; R = O, and R = CH_2), and (VIII). Acid hydrolysis of the methylanilino-derivative (VIII) rapidly gave phthalimide, aniline (isolated as phenylazo-2-naphthol), and *N*-methyl-

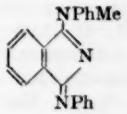
aniline (isolated as the *p*-nitroso-derivative), in approximately equivalent proportions. The same unsymmetrical *iso*indolenine (VIII) was formed by methylation of 1 : 3-diphenyliminoisoindoline (II; R = R′ = Ph) with sodamide and methyl iodide.

From the light-absorption data given in the Table it is possible tentatively to assign fine structures to some of the incompletely substituted compounds: these may have


(V)

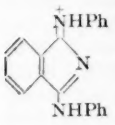

(VI)


(VII)


(VIII)

structures of either type *A* or *B*. In the oxo-series, the fixed 1-oxo*iso*indoline (I; R = Ph, R′ = Me), of type *A*, shows a maximum at 3020 Å (ε = 3800), whilst the fixed 1-oxo-*iso*indolenine (VI), of type *B*, shows additional maxima at the longer wave-lengths of 3270 and 3430 Å (ε = 3200). The derivatives (I; R = Ph, R′ = H) and (III; R = *m*-C_6H_4) have maxima (see Part I) at 3240, 3380 Å (ε = 4450), and at 3300, 3380 Å (ε = 8400), respectively, and both may therefore be presumed to exist (in the solvents named in the Table) in the tautomeric 3-amino-1-oxo*iso*indolenine form, *B*, corresponding with (VI). The same conclusion may be drawn for the other compounds (III).

The fixed 3-amino-1-imino*iso*indolenines (VII; R = O and CH_2) and (VIII) show maxima at 3680—3790 Å (ε = 11,000—14,000), but the parent 1 : 3-di-imino*iso*indoline (II; R = R′ = H), and the monobutyl and dibutyl derivatives show less intense maxima at the shorter wave-lengths of 3020—3200 Å (ε = 4000—6000). Hence it seems that these last three compounds exist largely in the *iso*indoline form, of type *A*. The spectra of the mono- and the di-phenylimino-derivatives (II; R = Ph, R′ = H and Ph) appear composite and suggest that these derivatives are tautomeric mixtures in solution (*A* ⇌ *B*); similar conclusions apply to the heterocyclic derivatives. In the naphthyl series (II; R = β-$C_{10}H_7$, R′ = H and β-$C_{10}H_7$) the *iso*indolenine form, *B*, appears to predominate, as judged from the intensity patterns: there is a rise in intensity at the maximum of longest wave-length, as there is in the spectra of (VII) and (VIII). The spectrum of 1 : 3-diphenyliminoisoindoline hydrochloride (see Part I) is broadly of this type, but there are differences in detail consistent with the cation's being a resonance hybrid (one bond structure is shown inset): there is absorption of somewhat higher intensity (ε = 20,000) at a longer wave-length (3980 Å) than for the related non-resonant compounds.



Studies on the fine structure of compounds of the same general type are being continued.

Experimental

Products from 3-Imino-1-oxoisoindoline.—(a) *From monoamines.* The oxo-imine (1 g.), 2-naphthylamine (1 g.), and ethanol (20 c.c.) were heated under reflux for 16 hr., and the solution was then chilled. The *3-2′-naphthylimino-1-oxoisoindoline* (0·84 g., 45%) crystallised from ethanol as yellow needles, m. p. 198—199° (Found: C, 79·75; H, 4·5; N, 10·5. $C_{18}H_{12}ON_2$ requires C, 79·4; H, 4·4; N, 10·3%).

3-Aminopyridine (0·5 g.), prepared from 3-bromopyridine (McElvain and Goese, *J. Amer. Chem. Soc.*, 1943, **65**, 2231) by Hertog and Wibaut's method (*Rec. Trav. chim.*, 1936, **55**, 122), 3-imino-1-oxo*iso*indoline (0·78 g.), and ethanol (10 c.c.) were heated under reflux for 22 hr., and the solution was then cooled. *1-Oxo-3-3′-pyridyliminoisoindoline* (0·79 g., 66·5%) crystallised from ethanol as very pale yellow needles, m. p. 222° (Found: C, 69·8; H, 4·3; N, 19·0. $C_{13}H_9ON_3$ requires C, 69·9; H, 4·1; N, 18·8%).

(b) *From diamines.* 2 : 7-Diaminonaphthalene (1 g.), 3-imino-1-oxo*iso*indoline (1·9 g.), and ethanol (25 c.c.) were heated under reflux for 1 day. The yellowish-brown product (1·1 g., 41%) was taken up in boiling pyridine, and the filtered solution evaporated until crystallisation

occurred. Sublimation of the solid at 300°/0·5 mm. afforded bright yellow crystals, m. p. 312°, of 2 : 7-*di*-(1-*oxo*-3-iso*indolinylideneamino*)*naphthalene* (III*a*) (Found : C, 74·8; H, 4·3; N, 14·0. $C_{26}H_{16}O_2N_4$ requires C, 75·0; H, 3·9; N, 13·5%).

3 : 5-Diaminopyridine (0·5 g.) [prepared in 57% yield from 3 : 5-dibromopyridine (McElvain and Goese, *loc. cit.*) and ammonia (*d* 0·88) in the presence of copper sulphate at 160° for 24 hr. (cf. Hertog and Wibaut, *loc. cit.*)] was heated with 3-imino-1-oxo*iso*indoline (1·35 g.) in ethanol (20 c.c.) under reflux for 40 hr. From 2-ethoxyethanol, the 3 : 5-*di*-(1-*oxo*-3-iso*indolinylideneamino*)*pyridine* (III*b*) (0·96 g., 57%) crystallised as very pale yellow needles, m. p. 343—344° (Found : C, 67·95; H, 3·8; N, 18·85. $C_{21}H_{13}O_2N_5$ requires C, 68·6; H, 3·6; N, 19·1%).

2 : 4-Diaminopyrimidine (0·2 g.) and 3-imino-1-oxo*iso*indoline (0·53 g.) were boiled in nitrobenzene (10 c.c.), ammonia being evolved vigorously at first and then slowly but steadily. After 17 hr., the clear solution was cooled. The 2 : 4-*di*-(1-*oxo*-3-iso*indolinylideneamino*)-*pyrimidine* (III*c*) (0·593 g., 88%) separated from nitrobenzene as very pale yellow needles, m. p. 288—289° (Found : C, 64·8; H, 3·55; N, 23·0. $C_{20}H_{12}O_2N_6$ requires C, 65·2; H, 3·3; N, 22·8%).

2 : 4-Diaminopyrimidine (0·5 g.) was heated under reflux in 2-ethoxyethanol (10 c.c.) with 3-imino-1-oxo*iso*indoline (0·67 g.) until the evolution of ammonia had almost ceased. When cooled, the solution deposited a crystalline mixture (0·65 g.), m. p. 235—258°. Fractional crystallisation from nitrobenzene gave in minute yield very pale yellow needles of 2 : 4-di-(1-oxo-3-*iso*indolinylideneamino)pyrimidine (Found : N, 21·8), m. p. and mixed m. p. 287°, and yellow 3-(4 ?-*amino*-2 ?-*pyrimidylimino*)-1-*oxo*iso*indoline*, m. p. 274° (Found : C, 59·7; H, 3·85; N, 29·1. $C_{12}H_9ON_5$ requires C, 60·2; H, 3·8; N, 29·3%). A third fraction had m. p. 264°, and light absorption max. (in ethanol) at 2510, 2650, 2800, 2900, 3300, 3450, 3650 Å (ε = 7900, 10,750, 7900, 7900, 6900, 6900, 6900, respectively).

Products from 1 : 3-*Di-imino*iso*indoline and Aniline.*—(a) *Preparations.* The di-imine (3 g.), aniline (4 g.), and ethanol (30 c.c.) were heated together under reflux. Ammonia was evolved. During the first 1—2 hr., the yellow monophenylimine (see below) separated, but this later redissolved, and the solution became darker. After 16 hr. the solution was evaporated, and the residue triturated repeatedly with light petroleum (b. p. 60—80°). The 1 : 3-*diphenylimino*iso*indoline* (3·82 g., 62%) crystallised from light petroleum (b. p. 40—60°) as pale yellow needles, m. p. 129° (Found : C, 80·8; H, 5·2; N, 14·2. $C_{20}H_{15}N_3$ requires C, 80·8; H, 5·1; N, 14·1%). The same compound (0·71 g.), m. p. and mixed m. p. 129°, was obtained by treatment of the deep yellow hydrochloride (Part I, *loc. cit.*) (1 g.) with boiling 0·1N-sodium hydroxide for 1 hr., and extraction of the product with boiling light petroleum (b. p. 40—60°).

1 : 3-Di-imino*iso*indoline (5 g.), aniline (3·2 g.), and ethanol (30 c.c.) were heated under reflux for 2 hr. A solid had then separated and evolution of ammonia had slackened. From ethanol, 1-*imino*-3-*phenylimino*iso*indoline* (6 g., 79%) separated as a yellow microcrystalline powder, m. p. 203° (decomp.) (Found : C, 76·0; H, 5·0; N, 19·1. $C_{14}H_{11}N_3$ requires C, 76·0; H, 5·0; N, 19·0%). When this imine (0·1 g.) was treated with aniline (0·1 g.) in boiling ethanol (5 c.c.) for 5 hr., ammonia was evolved. Passage of hydrogen chloride through the cooled solution precipitated 1 : 3-diphenyliminoisoindoline hydrochloride (0·12 g., 69%), which, after crystallisation from glacial acetic acid, had m. p. 276°, not depressed by authentic material (Part I, *loc. cit.*).

(b) *Hydrolyses.* 1-Imino-3-phenyliminoisoindoline (0·5 g.) was warmed for 5—10 sec. with concentrated hydrochloric acid (10 c.c.). Cold water was added, and the solution decanted from a little undissolved material into aqueous ammonia. The precipitate was crystallised from ethanol, and had m. p. 170° alone and in admixture with 1-oxo-3-phenyliminoisoindoline (Part I, *loc. cit.*).

When 1-imino-3-phenyliminoisoindoline (0·63 g.), ethanol (10 c.c.), and 2N-hydrochloric acid (20 c.c.) were heated together under reflux for 15 min. and the solution was cooled in ice, phthalimide separated. The filtrate was evaporated to dryness, and the residue taken up in 2N-hydrochloric acid (10 c.c.) and filtered from undissolved phthalimide (total yield, 0·39 g.; 0·93 mol.), m. p. 230—231°. The filtrate contained aniline (0·92 mol.), which was diazotised and coupled with 2-naphthol, yielding phenylazo-2-naphthol (0·65 g.), m. p. and mixed m. p. 131°.

Hydrolysis of 1 : 3-diphenyliminoisoindoline (0·5 g.) under similar conditions yielded phthalimide (0·23 g., 0·93 mol.) and aniline (1·80 mols.), isolated as phenylazo-2-naphthol (0·75 g.), the products being identified by mixed m. p.s.

Hydrolysis of 1-*Oxo*-3-*phenylimino*iso*indoline.*—(*a*) The compound (500 mg.), water (20 c.c.), and concentrated hydrochloric acid (1 c.c.) were heated together under reflux for 5 min. On

cooling of the solution in ice, phthalimide separated as needles (288 mg., 0·87 mol.), m. p. and mixed m. p. 230—231°.

(*b*) 1-Oxo-3-phenyliminoisoindoline (500 mg.), water (20 c.c.), and concentrated hydrochloric acid (0·25 c.c.) were heated together under reflux for 20 hr., and the solution which had evaporated somewhat was cooled. The white crystalline product (260 mg.), m. p. *ca.* 195—197°, was insoluble in cold aqueous sodium hydroxide. Recrystallisation from ethanol afforded needles of *N*-phenylphthalimide, m. p. 205° (Found: C, 75·25; H, 4·0; N, 6·4. Calc. for $C_{14}H_9O_2N$: C, 75·3; H, 4·1; N, 6·3%).

2-Methyl-1-oxo-3-phenyliminoisoindoline.—(*a*) 3-Imino-1-oxoisoindoline (1·46 g.) and methyl sulphate (1·26 g.; redistilled) were heated slowly to 65°, and the melt then cooled. From methanol, *3-imino-2-methyl-1-oxoisoindolinium methyl sulphate* crystallised with m. p. 243° (Found: C, 43·9; H, 4·4; N, 10·0; S, 11·8. $C_{10}H_{12}O_5N_2S$ requires C, 44·1; H, 4·4; N, 10·3; S, 11·8%). When its aqueous solution was boiled and then cooled, *N*-methylphthalimide separated (m. p. and mixed m. p. 134°; yield, quantitative).

The methyl sulphate (0·18 g.), aniline (0·5 c.c.), and methanol (10 c.c.) were heated under reflux for 17 hr. The solution was evaporated to a small volume and cooled. The *2-methyl-1-oxo-3-phenyliminoisoindoline* (0·11 g., 70%) formed pale yellow needles, m. p. 144°, from acetone (Found: C, 76·3; H, 5·2; N, 12·2. $C_{15}H_{12}ON_2$ requires C, 76·2; H, 5·1; N, 11·85%). When the compound (0·1 g.) was heated under reflux with 0·1N-hydrochloric acid (5 c.c.) for several minutes and the solution cooled, silky needles of *N*-methylphthalimide separated (0·06 g., 88%; m. p. and mixed m. p. 134°).

(*b*) 1-Oxo-3-phenyliminoisoindoline (0·5 g.), N-sodium hydroxide (20 c.c.), methyl sulphate (0·5 c.c.), and benzene (25 c.c.) were shaken together for 1·5 hr. The benzene layer was separated, washed with water, and evaporated. Recrystallisation of the residue from light petroleum (b. p. 60—80°) afforded pale yellow needles of the 2-methyl derivative, m. p. 141—142° and mixed m. p. 142—143°.

Addition of Amines to Phthalonitrile.—(*a*) Methanol (25 c.c.) in which sodium (5 mg.) had been dissolved, phthalonitrile (2·56 g.), and aniline (1·86 g.) were heated together under reflux for 4 hr. On cooling, 1-imino-3-phenyliminoisoindoline (2 g., 46%) separated, having m. p. and mixed m. p. 203° (decomp.).

(*b*) Sodium (5 mg.) was dissolved in methanol (25 c.c.), and phthalonitrile (2·56 g.) and *n*-butylamine (1·45 g.) were added. The solution was heated under reflux for 3 hr., filtered from a little phthalocyanine, and evaporated, and the residue was extracted with boiling benzene and triturated with ether and acetone. The residual *3-n-butylimino-1-iminoisoindoline* (3·8 g., 94%) separated from methanol (charcoal) as a colourless powder, m. p. 162—163° (decomp.) (Found: C, 71·4; H, 7·8; N, 20·9. $C_{12}H_{15}N_3$ requires C, 71·6; H, 7·5; N, 20·9%).

1 : 3-Di-n-butyliminoisoindoline.—(*a*) *3-n*-Butylimino-1-iminoisoindoline (1 g.) and *n*-butylamine (5 c.c.) were heated under reflux for 3 hr., during which ammonia was evolved. The solution was evaporated under reduced pressure and the residue crystallised from ether, to yield *1 : 3-di-n-butyliminoisoindoline* (1·15 g., 90%) as needles, m. p. 132° (Found: C, 74·2; H, 9·1; N, 15·9. $C_{16}H_{23}N_3$ requires C, 74·7; H, 9·0; N, 16·3%).

(*b*) The same product (0·83 g., 95%) was obtained from 1 : 3-di-iminoisoindoline (0·5 g.) and *n*-butylamine (5 c.c.), similarly.

Products from 1 : 3-Di-iminoisoindoline and β-Naphthylamine.—(a) *Preparations.* The di-imine (2 g.) and β-naphthylamine (5 g.) were heated in *n*-butanol (40 c.c.) under reflux until evolution of ammonia ceased. The solution was cooled, and the product which separated was washed with light petroleum (b. p. 80—100°). *1 : 3-Di-2′-naphthyliminoisoindoline* (4·2 g., 76%) crystallised from light petroleum (b. p. 80—100°) as yellow needles, m. p. 148—149° (Found: C, 84·3; H, 5·4; N, 10·7. $C_{28}H_{19}N_3$ requires C, 84·6; H, 4·8; N, 10·6%).

When 1 : 3-di-iminoisoindoline (3 g.) and β-naphthylamine (2·9 g.) were allowed to react together in boiling ethanol (30 c.c.) for 16 hr., and the solution cooled, *1-imino-3-2′-naphthyliminoisoindoline* separated (4·26 g., 76%), which, from ethanol containing a trace of ammonia, crystallised as yellow needles, m. p. 203—204° (decomp.) (Found: C, 80·0; H, 4·95; N, 15·3. $C_{18}H_{13}N_3$ requires C, 79·7; H, 4·8; N, 15·5%). Treatment of this imine (0·5 g.) with β-naphthylamine (0·3 g.) in boiling ethanol (10 c.c.) for 16 hr., evaporation of the solution, and trituration of the residue with light petroleum (b. p. 80—100°), yielded *1 : 3-di-2′-naphthyliminoisoindoline* (0·56 g., 76%), m. p. and mixed m. p. 148—149°.

(b) *Hydrolyses.* Stirring 1-imino-3-2′-naphthyliminoisoindoline (0·5 g.) with concentrated hydrochloric acid (10 c.c.) gave a red salt, rapidly converted into a yellow solid when the mixture was warmed. Water was added, and the solid warmed with aqueous ammonia and washed

with water. The 3-2′-naphthylimino-1-oxo*iso*indoline had m. p. 180—190°, raised on crystallisation from ethanol (charcoal) to 198—199° and not depressed by authentic material (above).

1-Imino-3-2′-naphthylimino*iso*indoline (0·5 g.), ethanol (10 c.c.), and concentrated hydrochloric acid (20 c.c.) were heated under reflux for 25 min. The solution was evaporated to dryness under reduced pressure, and the residue stirred with N-sodium hydroxide (10 c.c.) at 40° for 10 min., leaving insoluble β-naphthylamine (0·23 g., 0·87 mol.), m. p. and mixed m. p. 111° (acetyl derivative, m. p. 132°). The alkaline filtrate was acidified with concentrated hydrochloric acid, the precipitated phthalic acid collected, and the filtrate evaporated to dryness. Removal of inorganic salts with water (3 c.c.) left phthalic acid (total yield, 0·24 g., 0·78 mol.), m. p. 193° (decomp.). The *S*-benzylthiuronium salt had m. p. 158° alone and when mixed with the authentic salt of phthalic acid.

Hydrolysis of 1 : 3-di-2′-naphthylimino*iso*indoline (0·5 g.) for 2 hr. with boiling glacial acetic acid (10 c.c.) and concentrated hydrochloric acid (10 c.c.) yielded β-naphthylamine (0·38 g., 2·0 mols.) and phthalic acid (0·18 g., 0·86 mol.), separated and identified as before.

Products from 1 : 3-*Di-imino*iso*indoline and* 3-*Aminopyridine.*—(*a*) The di-imine (1 g.) and 3-aminopyridine (0·65 g.) in ethanol (10 c.c.) were heated under reflux for 17 hr., and the solution was then cooled. 1-*Imino*-3-3′-*pyridylimino*iso*indoline* (0·95 g., 62%) separated from ethanol as a bright yellow crystalline powder, m. p. 207° (Found: C, 70·4; H, 4·8; N, 25·4. $C_{13}H_{10}N_4$ requires C, 70·3; H, 4·5; N, 25·2%). The same product, m. p. and mixed m. p. 207°, was formed in 72% yield from an analogous reaction with 2 mols. of the aminopyridine (1·3 g.).

(*b*) The preceding product (1 g.) and 3-aminopyridine (0·43 g.) in butanol were heated under reflux for 24 hr., during which ammonia was evolved. The solution was evaporated. Trituration of the residue with light petroleum (b. p. 40—60°) afforded a pale yellow powder (1·18 g.), m. p. 142—147°, which crystallised from aqueous ethanol as solvated yellow needles, m. p. 122—123° (decomp.). After being dried at 100°/0·01 mm. for 2 hr., the 1 : 3-*di*-3′-*pyridylimino*iso*indoline* was very pale yellow and had m. p. 186° (Found: C, 72·0; H, 4·6; N, 23·3. $C_{18}H_{13}N_5$ requires C, 72·2; H, 4·4; N, 23·4%).

1 : 3-*Dipyrazinylimino*iso*indoline.*—Aminopyrazine (0·5 g.) (Weijlard, Tishler, and Erickson, *J. Amer. Chem. Soc.*, 1945, **67**, 802), 1 : 3-di-imino*iso*indoline (0·38 g.), and butanol (10 c.c.) were heated under reflux for 17 hr., ammonia being evolved. When cooled, the solution deposited yellowish-green crystals of 1 : 3-*dipyrazinylimino*iso*indoline* (0·52 g.), m. p. 250°, raised to 257° by recrystallisation from butanol or 2-ethoxyethanol (Found: C, 63·3; H, 3·6; N, 32·5. $C_{16}H_{11}N_7$ requires C, 63·8; H, 3·7; N, 32·55%).

Heating the dipyrazinylimino*iso*indoline with methyl iodide at 90—100° for 17 hr. gave the *dimethiodide*, which crystallised from aqueous ethanol as orange needles, m. p. 280—281° (Found: I, 43·6. $C_{18}H_{17}N_7I_2$ requires I, 43·4%).

The dimethiodide (0·456 g.) was heated with N-hydrochloric acid (10 c.c.) under reflux for 5 min., and the dark solution evaporated. The black tarry residue was boiled with concentrated hydrochloric acid, the solution was e aporated, the residue taken up in 2N-sodium hydroxide, and the solution treated twice with charcoal, concentrated, and acidified. The precipitate was washed with a little water, leaving phthalic acid (72 mg.), m. p. 190° (decomp.); the *S*-benzylthiuronium salt had m. p. and mixed m. p. 158°.

Derivatives of 3-*Amino*-1-*imino*iso*indolenine.*—(*a*) 3-Imino-1-oxo*iso*indoline (0·5 g.) was dissolved in hot ethanol (15 c.c.) and morpholine (0·5 c.c.; not distilled) added. After 2 days, the solution was evaporated and the residue triturated with ether, yielding crystals, m. p. 124—127°. From benzene (charcoal), the *amide morpholide* (V) of phthalic acid formed needles, m. p. 134° (Found: C, 62·0; H, 6·15; N, 11·9. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0; N, 12·0%). The same compound (1·03 g.), m. p. and mixed m. p. 133—135°, was obtained by shaking phthalimide (0·75 g.) with 1 : 1 aqueous morpholine (10 c.c.) and evaporating the solution under reduced pressure.

3-Imino-1-oxo*iso*indoline (1 g.) and morpholine (1 g., fractionated) were boiled together in ethanol (20 c.c.) for 17 hr., and the solution was evaporated to small bulk. Colourless needles (1·22 g.), m. p. 190—191°, separated. From ethanol or benzene, the 3-*morpholino*-1-*oxo*iso*indolenine* (VI) crystallised as needles, m. p. 191° (Found: C, 66·7; H, 5·8; N, 13·3. $C_{12}H_{12}O_2N_2$ requires C, 66·65; H, 5·6; N, 13·0%).

Similar interaction of 1 : 3-di-imino*iso*indoline (1 g.) and morpholine (1 g.; fractionated) in ethanol gave ammonia and a little phthalocyanine (identified spectroscopically). From the filtrate, on evaporation, needles separated (0·7 g.), having m. p. 125—130°, raised to 155—160°, and then to 191° on recrystallisation from ethanol and, later, benzene. The final product was identical (mixed m. p.) with 3-morpholino-1-oxo*iso*indolenine.

(*b*) 1-Imino-3-phenylimino*iso*indoline (1 g.), morpholine (1 c.c.; redistilled), and ethanol (20 c.c.) were heated under reflux for 17 hr. The hot solution was treated with charcoal, evaporated to small bulk, and cooled. The 3-*morpholino*-1-*phenylimino*iso*indolenine* (VII; R = O) (0·5 g.) crystallised from benzene–light petroleum (b. p. 60—80°) as yellow needles, m. p. 165° (Found: C, 74·3; H, 6·1; N, 14·1. $C_{18}H_{17}ON_3$ requires C, 74·2; H, 5·9; N, 14·4%).

(*c*) Similar interaction of 1-imino-3-phenyliminoisoindoline (1 g.) and piperidine (1 c.c.) in ethanol gave a viscous red oil, which solidified partly when triturated with light petroleum (b. p. 40—60°). The mass was drained on porous tile overnight, then dissolved in a minimum of benzene, and the solution diluted to 50 c.c. with light petroleum (b. p. 60—80°). 1-*Phenylimino*-3-*piperidino*iso*indolenine* (VII; R = CH_2) (0·2 g.) slowly separated, and on recrystallisation from light petroleum (b. p. 100—120°) formed yellow needles, m. p. 118° (Found: C, 79·0; H, 6·6; N, 14·2. $C_{19}H_{19}N_3$ requires C, 78·8; H, 6·6; N, 14·5%).

(*d*) 1-Imino-3-phenyliminoisoindoline (1 g.), *N*-methylaniline (1 c.c.), and ethanol (20 c.c.) were heated under reflux for 24 hr. The solution was evaporated under reduced pressure and ether added. Starting material (0·45 g.), m. p. 200—201°, was filtered off, the filtrate evaporated, and the residual gum triturated with light petroleum (b. p. 60—80°) (50 c.c.). When left at room temperature the extract slowly deposited a yellow crystalline solid: the first crop (1 hr.), which softened from 120°, was rejected, and the second crop (90 mg.) (several days), m. p. 120—124°, was recrystallised several times from ethanol–water. The 3-*N*-*methylanilino*-1-*phenylimino*iso*indolenine* (VIII) formed yellow prisms, m. p. 128° (Found: C, 80·2; H, 5·55; N, 13·5. $C_{21}H_{17}N_3$ requires C, 80·4; H, 5·7; N, 13·9%).

The same compound (mixed m. p. undepressed) was prepared by heating 1:3-diphenyliminoisoindoline (1 g.) in dry benzene (40 c.c.) with powdered sodamide (0·3 g.) for 1·5 hr. and then with methyl iodide (3 c.c.) until the mixture began to darken (*ca.* 20 min.); the mixture was then shaken with several lots of water, and the benzene layer dried and evaporated (yield, 0·84 g.; m. p. 122—123°, raised to 127—128° on recrystallisation).

When 3-*N*-methylanilino-1-phenyliminoisoindolenine (96·9 mg.) was heated under reflux with 2N-hydrochloric acid (5 c.c.) for 3 min., and the solution cooled in ice, phthalimide crystallised (33·7 mg., 0·73 mol.; m. p. and mixed m. p. 231—232°). The filtrate was treated slowly at *ca.* 5° with sodium nitrite (60 mg.) in water. After 10 min., the oil which had separated was taken up in ether (*E*). The aqueous layer was added to 2-naphthol (150 mg.) in ice-cold 2N-sodium hydroxide (6 c.c.), yielding phenylazo-2-naphthol (74·1 mg., 0·96 mol.), m. p. 126—127°. The extract *E* was dried ($MgSO_4$) and treated with dilute ethanolic hydrogen chloride (1 c.c.) for 30 min., then washed with aqueous sodium carbonate and water. Evaporation of the ether yielded *N*-methyl-*p*-nitrosoaniline, which crystallised from benzene as greenish-yellow plates (29·5 mg., 0·7 mol.), m. p. and mixed m. p. 114—115°.

We gratefully acknowledge a maintenance grant (to P. F. C.) from the Ministry of Education, and gifts of chemicals from Imperial Chemical Industries Limited, Dyestuffs Division. Microanalyses and spectrographic determinations were performed in the micro-analytical (Mr. F. H. Oliver) and the spectrographic (Mrs. A. I. Boston) laboratories of this Department.

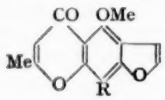
Department of Organic Chemistry, Imperial College of Science and Technology, South Kensington, London, S.W.7. [*Received, July 14th*, 1953.]

723. *Furanochromones derived from Quinol.*

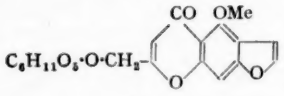
By G. R. Ramage and C. V. Stead.

5-Methoxycoumaran-3-one (III; R = Me) has been reduced to the coumarone (IV) and to the coumaran (V; R = Me). Simultaneous acetylation and demethylation of this coumaran has led to 6-acetyl-5-hydroxycoumaran (VI; R = H). This compound and its dehydrogenation product have given, by extension of the side-chain and subsequent cyclisation, 4′ : 5′-dihydrofurano(2′ : 3′-6 : 7)chromones (XI; R = Me, H, or CO_2H) and the corresponding furanochromones (XIII).

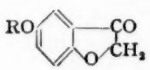
The seeds of *Ammi visnaga*, a plant growing wild in the Eastern Mediterranean regions, have been shown to contain three compounds containing a furanochromone nucleus (see Huttrer and Dale, *Chem. Reviews*, 1951, **48**, 543). These are kellin (I; R = OMe), visnagin (I; R = H), and kellol glucoside (II). The first syntheses of one of these compounds, namely, kellin, occurred recently (Clarke and Robertson, *J.*, 1949, 302; Baxter, Ramage, and Timson, *ibid.*, p. S 30). Since the review by Huttrer and Dale (*loc. cit.*) visnagin has been synthesised by Gruber and Horváth (*Monatsh.*, 1950, **81**, 819), and kellol by Geissman and Bolger (*J. Amer. Chem. Soc.*, 1951, **73**, 5875).



(I)



(II)



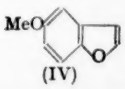
(III)

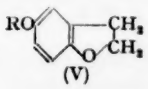
In all these furanochromes, the oxygen atoms which are involved in heterocyclic ring formation are situated in *meta*-positions. The preparation of compounds in which the heterocyclic oxygen atoms are *para* to one another is being undertaken in order to see whether the *meta*-orientation is of importance in determining the pharmacological activity. The simplest furanochromone of this type would result from the use of quinol as starting material.

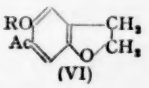
Quinol dimethyl ether (Dyson, George, and Hunter, *J.*, 1927, 440) underwent reaction with chloroacetyl chloride in carbon disulphide solution and gave 2-hydroxy-5-methoxyphenacyl chloride, cyclisation of which yielded 5-methoxycoumaran-3-one (III; R = Me) (von Auwers and Pohl, *Annalen*, 1914, **405**, 281). Hydrogenation of this coumaranone at atmospheric pressure in the presence of Raney nickel gave a mixture from which 5-methoxycoumarone (IV) was isolated. This compound has been previously described by Stoermer (*Annalen*, 1900, **312**, 335), who prepared it by refluxing *p*-methoxyphenoxyacetaldehyde diethyl acetal with zinc chloride in acetic acid, and also, in a higher state of purity, by Tanaka (*J. Amer. Chem. Soc.*, 1951, **73**, 872) who obtained it from 2-hydroxy-5-methoxybenzaldehyde by condensation with ethyl bromomalonate, followed by cyclisation and decarboxylation.

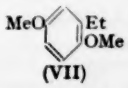
On hydrogenation with Raney nickel at 60°/50 atm., (III; R = Me) yielded 5-methoxycoumaran (V; R = Me). This was a liquid which readily formed a highly crystalline dinitro-compound, presumably 5-methoxy-4 : 6-dinitrocoumaran. The coumaran (V; R = Me) was treated with acetyl chloride and aluminium chloride in carbon disulphide solution, and the product was separated into phenolic and non-phenolic fractions. The former gave 6-acetyl-5-hydroxycoumaran (VI; R = H) whereas the latter furnished a liquid ketone. Formation of tar made purification of both components difficult, but when reaction was effected in ether (cf. Oliverio and Lugli, *Gazzetta*, 1948, **78**, 16) the phenolic component was obtained in higher yield and in a purer state. The non-phenolic fraction, which distilled over the same temperature range as that from the reaction in carbon disulphide, then solidified to give 6-acetyl-5-methoxycoumaran (VI; R = Me). The relation of these two compounds as a phenol and its methyl ether was demonstrated

by demethylating (VI; R = Me) with aluminium chloride in refluxing ether and yielded (VI; R = H), which on methylation re-formed (VI; R = Me).

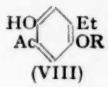

(IV)

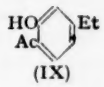

(V)

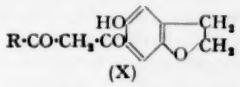

(VI)


(VII)

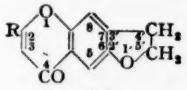
The formulation of the product from the Friedel–Crafts reaction on (V; R = Me) as 6-acetyl-5-hydroxycoumaran was based on the fact that the structurally similar ethylquinol dimethyl ether (VII) was acetylated, under the conditions used for (V; R = Me), in the analogous position and gave 4-ethyl-2-hydroxy-5-methoxyacetophenone (VIII; R = Me). The orientation of (VIII; R = Me) followed from its preparation from *m*-ethylphenyl acetate by means of a Fries rearrangement which gave (IX), followed by nuclear oxidation with ammonium persulphate in alkaline solution giving (VIII; R = H), the monomethyl ether of which was identical with (VIII; R = Me).

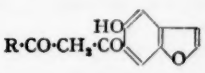

(VIII)

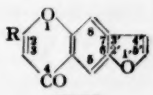

(IX)


(X)

In the preparation of dihydrofuranochromones from (VI; R = H), the second heterocyclic ring system was readily built up by the method of Cheema, Gulati, and Venkataraman (*J.*, 1932, 925). Treatment of (VI; R = H) with ethyl acetate in the presence of powdered sodium gave, after crystallisation from water, 4′ : 5′-dihydro-2-methylfurano(2′ : 3′-6 : 7)chromone (XI; R = Me) instead of the expected (X; R = Me). The latter compound was probably formed first, but, during the heating inherent in crystallisation from water, cyclised to the chromone. Use of ethyl oxalate instead of ethyl acetate in the Claisen condensation gave the diketo-ester (X; R = CO_2Et). This compound cyclised to 4′ : 5′-dihydrofurano(2′ : 3′-6 : 7)chromone-2-carboxylic acid (XI; R = CO_2H). Decarboxylation of this acid was readily accomplished by heating it *in vacuo*, giving 4′ : 5′-dihydrofurano(2′ : 3′-6 : 7)chromone (XI; R = H).


(XI)


(XII)


(XIII)

Subliming (VI; R = H) under reduced pressure through an electrically heated column of palladium–Norit (30%), prepared as described by Linstead and Thomas (*J.*, 1940, 1127), dehydrogenated it to 6-acetyl-5-hydroxycoumarone which undergoes Claisen condensations and cyclisations in the same manner as does the coumaran (VI; R = H). Thus, with ethyl acetate it gave 2-methylfurano(2′ : 3′-6 : 7)chromone (XIII; R = Me), and with ethyl oxalate the diketo-ester (XII; R = CO_2Et). The latter compound cyclised in acid to furano(2′ : 3′-6 : 7)chromone-2-carboxylic acid (XIII; R = CO_2H) which was smoothly decarboxylated *in vacuo* to furano(2′ : 3′-6 : 7)chromone (XIII; R = H).

Experimental

5-Methoxycoumarone (IV).—5-Methoxycoumaran-3-one (10 g.) (von Auwers and Pohl, *loc. cit.*) was hydrogenated in ethanol (100 c.c.) in presence of Raney nickel catalyst (35 c.c.) at 60° for 4 hr. and then cooled. Filtration followed by distillation of the solvent left an oil which was fractionated. The portion, b. p. 156—160°/60 mm. (5·5 g., 60%), solidified in a refrigerator. It was crystallised from aqueous ethanol and sublimed at 50°/10^{-2} mm., to yield 5-methoxycoumarone as colourless needles, m. p. 31·5° (Found: C, 72·5; H, 5·4. Calc. for $C_9H_8O_2$: C, 73·0; H, 5·4%).

5-Methoxycoumaran (V; R = Me).—5-Methoxycoumaran-3-one (50 g.) and Raney nickel catalyst (20 c.c.) together with ethanol (400 c.c.) were agitated at 80° under hydrogen at 50 atm. for 4 hr. Cooling, filtration, evaporation, and fractionation gave *5-methoxycoumaran* (46 g., 92%) as a colourless oil, b. p. 134°/20 mm. (Found : C, 72·2; H, 6·8. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%).

5-Methoxy-4 : 6-dinitrocoumaran.—By cautiously adding a solution of nitric acid (*d* 1·5; 1 c.c.) in glacial acetic acid (3 c.c.) to one of 5-methoxycoumaran (2 g.) in glacial acetic acid (3 c.c.), *5-methoxy-4 : 6-dinitrocoumaran*, obtained on dilution, formed light yellow needles, m. p. 107°, from methanol (Found : C, 45·4; H, 3·5. $C_9H_8O_6N_2$ requires C, 45·0; H, 3·4%).

6-Acetyl-5-methoxycoumaran (VI; R = Me) *and 6-Acetyl-5-hydroxycoumaran* (VI; R = H).—(*a*) Freshly sublimed aluminium chloride (6 g.) was added to a solution of 5-methoxycoumaran (6 g.) in carbon disulphide (40 c.c.), followed by a solution of acetyl chloride (5 c.c.) in carbon disulphide (10 c.c.). The mixture was refluxed for 20 hr., the solvent distilled off, and the residue powdered and added to ice (100 g.) and concentrated hydrochloric acid (5 c.c.). The resulting emulsion was extracted with ether, and the ethereal layer filtered and shaken with sodium hydroxide solution (25 c.c., 20%). The residual oil from the ethereal layer was distilled under reduced pressure (b. p. 153—158°/20 mm.) to yield an oil (2 g.), believed to be 6-acetyl-5-methoxycoumaran. After the alkaline layer had been freed from ether, it was cooled and acidified with 20% hydrochloric acid (20 c.c.). The fawn precipitate crystallised from ligroin, to yield yellow needles of *6-acetyl-5-hydroxycoumaran* (1·4 g., 20%), m. p. 109—111° (Found : C, 67·5; H, 5·8. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%).

(*b*) Freshly sublimed aluminium chloride (30 g.) was dissolved in anhydrous ether (250 c.c.) with cooling. 5-Methoxycoumaran (20 g.) was then added, followed by acetyl chloride (10 c.c.), and the resulting mixture refluxed overnight. After cooling, ice (200 g.) and concentrated hydrochloric acid (20 c.c.) were added and the ethereal layer removed. This was extracted with sodium hydroxide solution (200 c.c., 5%) and the residual oil from the dried ethereal layer was distilled, to yield a colourless oil, b. p. 156°/20 mm., which solidified to a lemon-yellow solid. *6-Acetyl-5-methoxycoumaran* (5·4 g., 21%) crystallised from methanol in pale yellow needles, m. p. 82° (Found : C, 69·1; H, 6·2. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%). Its *2 : 4-dinitrophenylhydrazone*, prepared in methanol, crystallised from ethyl acetate in dark red needles, m. p. 212° (Found : C, 55·5; H, 4·4. $C_{17}H_{16}O_6N_4$ requires C, 54·8; H, 4·3%).

The alkaline layer was freed from ether and acidified with concentrated hydrochloric acid (25 c.c.). The pale yellow precipitate crystallised from ligroin, to yield 6-acetyl-5-hydroxycoumaran (8·5 g., 33%), m. p. 109—111°. Its *2 : 4-dinitrophenylhydrazone*, prepared in water, crystallised from 2-ethoxyethanol in red needles, m. p. 240° (Found : C, 53·3; H, 3·9. $C_{16}H_{14}O_6N_4$ requires C, 53·6; H, 3·9%).

Demethylation of 6-Acetyl-5-methoxycoumaran.—6-Acetyl-5-methoxycoumaran (1 g.) was added to a solution of freshly sublimed aluminium chloride (5 g.) in anhydrous ether (50 c.c.). The solution was refluxed for 20 hr., cooled, and added to ice (20 g.). An orange precipitate, presumably the aluminium chloride complex, dissolved on addition of concentrated hydrochloric acid (5 c.c.) and warming under reflux for 30 min. The ethereal layer was extracted with sodium hydroxide solution (20 c.c., 5%). The separated alkaline layer, freed from ether, was added to ice-cold concentrated hydrochloric acid (5 c.c.), and the precipitated phenol filtered off. Crystallisation from ligroin yielded 6-acetyl-5-hydroxycoumaran as yellow needles (0·3 g., 36%), m. p. 109—111°, identical with the product described above.

Ethylquinol Dimethyl Ether (VII).—To ethylquinol (30 g.) in potassium hydroxide solution (150 g., 33%), methyl sulphate (60 c.c.) was added in portions during 15 min. with shaking and ice-cooling. The mixture was shaken for a further 15 min. and then warmed on a steam-bath for 1 hr. The product was removed by steam-distillation and extracted from the distillate with carbon tetrachloride. Evaporation of the dried extract left *ethylquinol dimethyl ether* (26 g., 70%), b. p. 232° (Found : C, 72·8; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·5%).

4-Ethyl-2-hydroxy-5-methoxyacetophenone (VIII; R = Me).—Ethylquinol dimethyl ether (2·6 g.) was added to freshly sublimed aluminium chloride (3·4 g.) in anhydrous ether (30 c.c.). Acetyl chloride (1·3 g.) was added and the resulting mixture refluxed overnight. Ice (50 g.) and concentrated hydrochloric acid (5 c.c.) were added to the cooled solution, and the yellow ethereal layer removed and extracted with potassium hydroxide solution (20 c.c., 20%). The alkaline layer was freed from ether and acidified with concentrated hydrochloric acid. The light yellow precipitate crystallised from methanol, yielding *4-ethyl-2-hydroxy-5-methoxyacetophenone* as pale lemon-yellow needles (1·7 g., 27%), m. p. 60° (Found : C, 68·1; H, 7·1. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%). The *2 : 4-dinitrophenylhydrazone*, prepared in methanol, formed red needles

(from ethyl acetate), m. p. 229° (Found: C, 54·3; H, 4·7. $C_{17}H_{18}O_6N_4$ requires C, 54·5; H, 4·8%).

m-*Ethylphenyl Acetate*.—*m*-Ethylphenol (56 g.) and acetyl chloride (75 c.c.) (1 hr. on a water-bath) gave *m*-ethylphenyl acetate (67 g., 89%), b. p. 234°.

2-*Hydroxy*-4-*ethylacetophenone* (IX).—*m*-Ethylphenyl acetate (45 g.) was mixed with powdered aluminium chloride (56 g.) and, after evolution of hydrogen chloride had ceased, the mixture was quickly heated to 120° in an oil-bath and the temperature was then raised to 165° during 15 min. Ice (500 g.) and concentrated hydrochloric acid (50 c.c.) were added and the light brown oil which separated was extracted with ether. Removal of the solvent from the dried ethereal solution left an oil which was fractionated. The fraction, b. p. 140—144°/20 mm., gave 4-*ethyl*-2-*hydroxyacetophenone* as a light yellow oil (37 g., 81%), b. p. 142°/20 mm. (Found: C, 73·0; H, 7·4. $C_{10}H_{12}O_2$ requires C, 73·1; H, 7·4%). This was followed by a fraction of b. p. 195—200°/20 mm. which solidified to give 2-ethyl-4-hydroxyacetophenone, crystallising from carbon tetrachloride in colourless leaflets (3 g., 7%), m. p. 102° (Kenner and Statham, *J.*, 1935, 302, give m. p. 102°).

4-*Ethyl*-2 : 5-*dihydroxyacetophenone* (VIII; R = H).—4-Ethyl-2-hydroxyacetophenone (17·6 g.) was dissolved in potassium hydroxide solution (10%, 200 c.c.), and pyridine (50 c.c.) was added to keep the potassium salt in solution. Ammonium persulphate solution (28·2 g., in 300 c.c. of water) was added dropwise during 4 hr. with stirring and ice-cooling. The solution was left overnight, made just acid to Congo-red with concentrated hydrochloric acid, and extracted with chloroform to remove unchanged material (10 g.). The aqueous solution was then made strongly acid with concentrated hydrochloric acid (50 c.c.), and the mixture heated on a steam-bath for 30 min. On cooling, a pale yellow solid crystallised. This was filtered off and recrystallised from light petroleum (b. p. 60—80°), to yield 4-*ethyl*-2 : 5-*dihydroxyacetophenone* as yellow plates (0·45 g.), m. p. 100°, giving a transient green colour followed by a brown precipitate with ferric chloride solution (Found: C, 66·7; H, 6·8. $C_{10}H_{12}O_3$ requires C, 66·7; H, 6·7%). Extraction with ether failed to give a further quantity of pure material.

4-*Ethyl*-2-*hydroxy*-5-*methoxyacetophenone* (VIII; R = Me).—4-Ethyl-2 : 5-dihydroxyacetophenone (0·4 g.), anhydrous potassium carbonate (2·0 g.), methyl sulphate (0·32 g.), and acetone (10 c.c.) were heated on a water-bath under reflux for 5 hr. The acetone was then distilled off and dilute hydrochloric acid (20 c.c., from 3 c.c. of concentrated acid) added. The fawn solid crystallised from methanol, yielding 4-ethyl-2-hydroxy-5-methoxyacetophenone (0·2 g., 47%) as pale lemon-yellow needles, m. p. 58°, undepressed on admixture with a sample obtained by Friedel–Crafts acetylation of ethylquinol dimethyl ether as above, and gave the same 2 : 4-dinitrophenylhydrazone, m. p. 229°.

4′ : 5′-*Dihydro*-2-*methylfurano*(2′ : 3′-6 : 7)*chromone* (XI; R = Me).—6-Acetyl-5-hydroxycoumaran (1 g.), powdered sodium (0·6 g.), and dry ethyl acetate (10 c.c.) were heated under reflux on a steam-bath for 3 hr. and the excess of ethyl acetate then removed by distillation. The yellow sodium salt which remained was decomposed by ice (10 g.) and glacial acetic acid (0·5 c.c.), and the precipitate filtered off. On crystallisation from water, 4′ : 5′-*dihydro*-2-*methylfurano*(2′ : 3′-6 : 7)*chromone* formed colourless needles (0·5 g., 44%), m. p. 139° (Found: C, 71·7; H, 4·8. $C_{12}H_{10}O_3$ requires C, 71·3; H, 5·0%).

6-(β-*Ethoxycarbonyl*-β-*oxopropionyl*)-5-*hydroxycoumaran* (X; R = CO_2Et).—6-Acetyl-5-hydroxycoumaran (2 g.) was added to powdered sodium (1·2 g.), covered with dry ethyl oxalate (10 c.c.), and the mixture heated on a water-bath until vigorous evolution of hydrogen commenced. At this point, the reaction vessel was removed from the source of heat until the reaction had moderated. Heating was then continued until evolution of gas had ceased and for a further 30 min. (2 hr. in all). The dark red mass was then macerated with benzene (20 c.c.), and the insoluble sodium salt filtered off, washed with benzene, and dried. It was decomposed with ice (20 g.) and acetic acid (1 c.c.), and the precipitate removed. 6-(β-*Ethoxycarbonyl*-β-*oxopropionyl*)-5-*hydroxycoumaran* formed colourless needles, m. p. 133—134° (2·3 g., 74%), from ethanol (Found: C, 60·5; H, 5·2. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·1%).

4′ : 5′-*Dihydrofurano*(2′ : 3′-6 : 7)*chromone*-2-*carboxylic Acid* (XI; R = CO_2H).—The foregoing ester (1 g.) was heated with concentrated hydrochloric acid (1·25 c.c.) and glacial acetic acid (6 c.c.) for 1½ hr. After cooling, the crystalline precipitate of 4′ : 5′-*dihydrofurano*(2′ : 3′-6 : 7)*chromone*-2-*carboxylic acid* was filtered off and recrystallised from a large volume of glacial acetic acid, forming colourless needles (0·6 g., 72%), m. p. 307° (decomp.) (Found: C, 62·7; H, 3·6. $C_{12}H_8O_5$ requires C, 62·1; H, 3·5%).

4′ : 5′-*Dihydrofurano*(2′ : 3′-6 : 7)*chromone* (XI; R = H).—4′ : 5′-Dihydrofurano(2′ : 3′-6 : 7)-chromone-2-carboxylic acid (0·75 g.) was placed in a bent test-tube, covered with a glass wool

plug, and heated. Smooth decarboxylation took place at a pressure of 4 mm. and the resulting dihydrofuranochromone sublimed, and was resublimed at 150°/10^{-4} mm. to yield colourless *4′ : 5′-dihydrofurano*(2′ : 3′-6 : 7)*chromone* (0·55 g., 83%), m. p. 170° (Found : C, 70·4; H, 4·3. $C_{11}H_8O_3$ requires C, 70·2; H, 4·3%).

6-Acetyl-5-hydroxycoumarone.—6-Acetyl-5-hydroxycoumaran (2 g.) was sublimed at 100° into a 25″ column of 30% palladium–Norit (0·8 g.) prepared as described by Linstead and Thomas (*J.*, 1940, 1127) supported on glass wool (3·0 g.) and maintained at 150° by means of an external heating coil. Sublimation was carried out at 10^{-4} mm. When the reactant reached the catalyst, the pressure fell to about 10^{-2} mm., but after approx. 3 hr. the initial pressure was restored. The product was collected on a cold finger at the top of the catalyst tube. *6-Acetyl-5-hydroxycoumarone* condensed as a pale lemon-coloured solid (1·95 g., 98%) crystallising in squat needles, m. p. 89°, from ligroin (Found : C, 67·7; H, 4·5. $C_{10}H_8O_3$ requires C, 68·2; H, 4·6%).

2-Methylfurano(2′ : 3′-6 : 7)*chromone* (XIII; R = Me).—6-Acetyl-5-hydroxycoumarone (2 g.) was added to dry ethyl acetate (20 c.c.) and powdered sodium (1·2 g.), and the whole refluxed on a water-bath for 3 hr. The excess of ethyl acetate was then distilled off and the sodium salt which remained was decomposed with ice (10 g.) and glacial acetic acid (0·5 c.c.). The precipitate crystallised from water, giving *2-methylfurano*(2′ : 3′-6 : 7)*chromone* as colourless needles (1·0 g., 44%), m. p. 167°. Further purification was effected by sublimation (140°/10^{-4} mm.), this raising the m. p. to 169° (Found : C, 71·7; H, 4·0. $C_{12}H_8O_3$ requires C, 72·0; H, 4·0%).

6-(β-Ethoxycarbonyl-β-oxopropionyl)-5-hydroxycoumarone (XII; R = CO_2Et).—6-Acetyl-5-hydroxycoumarone (2 g.) was added to ethyl oxalate (10 c.c.) and powdered sodium (1·2 g.) and the mixture warmed on a steam-bath until reaction commenced. The flask was then removed from the source of heat until the evolution of gas had moderated, then heated again until evolution of hydrogen had ceased and for a further 30 min. (about 2½ hr. in all). The cooled mixture was then macerated with benzene, and the dark red sodium salt filtered off and dried. The salt was decomposed with ice (20 g.) and acetic acid (1·5 c.c.) and the precipitate removed. 6-(β-Ethoxycarbonyl-β-oxopropionyl)-5-hydroxycoumarone was obtained as a light brown solid (2·8 g., 89%), m. p. 145°, and was not further purified.

Furano(2′ : 3′-6 : 7)*chromone-2-carboxylic acid* (XIII; R = CO_2H).—Crude diketo-ester (2 g.) was refluxed in glacial acetic acid (12 c.c.) containing concentrated hydrochloric acid (2·5 c.c.) for 1½ hr. and then cooled. The crystalline precipitate was removed and recrystallised from glacial acetic acid. *Furano*(2′ : 3′-6 : 7)*chromone-2-carboxylic acid* formed colourless rosettes (1·1 g., 66%), m. p. 341° (decomp.) (Found : C, 62·0; H, 3·1. $C_{12}H_6O_5$ requires C, 62·6; H, 2·6%).

Furano(2′ : 3′-6 : 7)*chromone* (XIII; R = H).—Furano(2′ : 3′-6 : 7)chromone-2-carboxylic acid (0·75 g.) was decarboxylated as above. The material which sublimed was removed and resublimed (100°/10^{-4} mm.), giving colourless needles of *furano*(2′ : 3′-6 : 7)*chromone* (0·55 g., 83%), m. p. 149° (Found : C, 70·5; H, 3·7. $C_{11}H_6O_3$ requires C, 71·0; H, 3·2%).

The authors are grateful for an I.C.I. Research Scholarship awarded to one of them (C. V. S.) by the Huddersfield Education Authority.

HUDDERSFIELD TECHNICAL COLLEGE. [*Received, July 20th,* 1953.]

724. *Perfluoroalkyl Grignard and Grignard-type Reagents. Part III.* Heptafluoro-n-propylzinc iodide.*

By R. N. Haszeldine and E. G. Walaschewski.

Reaction of heptafluoroiodopropane with zinc in a solvent such as dioxan, diethyl ether, dibutyl ether, or tetrahydropyran (Lewis bases) yields heptafluoropropylzinc iodide (50—60%). The product from reaction in dioxan may be isolated as $C_3F_7{\cdot}ZnI,C_4H_8O_2$, and this can be converted into unsolvated heptafluoropropylzinc iodide. Heptafluoropropane, hexafluoropropene, and perfluoro-*n*-hexane are by-products, and the yield of the last compound increases with increase in reaction temperature. Heptafluoropropylzinc iodide is less reactive than heptafluoropropylmagnesium iodide. Some of its reactions are recorded.

The preparation and reactions of heptafluoropropylmagnesium iodide have been described in Parts I (*J.*, 1952, 3423) and II *; the Grignard reagent is reactive, and unstable at temperatures much above 0°. The preparation of a Grignard-type reagent, heptafluoropropylzinc iodide, is now described (for a preliminary note see *Nature*, 1951, **168**, 1028; also work by Miller, Amer. Chem. Soc. Meeting, Atlantic City, 1952).

Zinc fails to react with heptafluoroiodopropane in the absence of a solvent at temperatures up to 250°; at higher temperatures increasing amounts of perfluoro-*n*-hexane are formed, doubtless by combination of heptafluoropropyl radicals, and the formation of bisheptafluoropropylzinc cannot be detected. Reaction does not occur in perfluoromethyl*cyclo*hexane, perfluoro-*n*-butyl ether, or perfluorotributylamine solution, and a basic solvent (in the Lewis sense) is necessary; ethyl ether, butyl ether, dioxan, or tetrahydropyran have been found suitable. As shown in another series (Haszeldine, *J.*, 1953, 2622) a neutral-molecule base, B, combines with a fluoroalkyl iodide, RI, to give a molecular compound of the type (RI),B in which there is transfer of an electron from B to RI with formation of a weak covalent bond between the odd electron of B^+ and $(RI)^-$. It is suggested that the carbon–iodine bond in such a complex approaches more to that in, say, ethyl iodide in character, *i.e.*, it will undergo much more readily reactions which involve heterolytic fission of the bond, notably the formation of organometallic compounds. It was shown in Part I that the yield of heptafluoropropylmagnesium iodide increased with increase in basicity of the solvent.

As observed for the formation of heptafluoropropylmagnesium iodide, the yield of heptafluoropropylzinc iodide is markedly dependent on the reaction temperature, with a maximum (50—60%) at *ca.* 0°. Reaction of concentrated solutions of heptafluoroiodopropane with zinc gives low yields, and an iodide–solvent ratio of at least 1 : 5 should be employed. The by-products are heptafluoropropane, hexafluoropropene, and perfluoro-*n*-hexane. The first two probably arise by reaction or decomposition of the heptafluoropropyl anion:

$$C_3F_7{\cdot}ZnI \longrightarrow C_3F_7^-;\ C_3F_7^- \xrightarrow{\text{solvent}} C_3F_7H;\ CF_3{-}\underset{F}{CF}{-}CF_2^- \longrightarrow CF_3{\cdot}CF{:}CF_2 + F^-$$

The yield of perfluoro-*n*-hexane increases rapidly with increase in reaction temperature. In Part I (*loc. cit.*) the formation of this compound was visualised as a bimolecular reaction of heptafluoroiodopropane with heptafluoropropylmagnesium iodide, but now that molecular compound formation has been established for the perfluoroiodoalkanes, it seems probable that the valency structure of the carbon–iodine bond of heptafluoroiodopropane is sufficiently changed in solution to enable a Wurtz-type reaction to proceed without, necessarily, formation of the fluoroalkylzinc iodide as intermediate.

The presence of heptafluoropropylzinc iodide is shown by the liberation of heptafluoropropane when aqueous reagents are added. To prove that the heptafluoropropane

* Part II, Haszeldine, *J.*, 1953, 1748.

was not produced by the reduction of heptafluoroiodopropane in solution or as a complex, heptafluoropropylzinc iodide itself has been isolated. The solvated organometallic compound (one mol. of dioxan) is converted into the pure heptafluoropropylzinc iodide by fractional molecular sublimation; handling losses are high, and the organometallic compound should normally be used in solution. There is no indication of an equilibrium, $2C_3F_7{\cdot}ZnI \rightleftharpoons (C_3F_7)_2Zn + ZnI_2$.

When unsolvated heptafluoropropylzinc iodide is heated, hexafluoropropene is formed; this reaction is similar to the formation of hexafluoropropene by pyrolysis of sodium heptafluorobutyrate (*J.*, 1952, 4259), and the heptafluoropropyl anion is probably the intermediate in each case. Aqueous sodium hydroxide converts the fluoroalkylzinc iodide quantitatively into heptafluoropropane. Water reacts similarly when hot, but much more slowly at room temperature, revealing a difference from heptafluoropropylmagnesium iodide. Chlorine converts the zinc compound into 1-chloroheptafluoropropane, whereas anhydrous hydrogen chloride gives heptafluoropropane. The reactions prove that the constitution of the organometallic compound is $C_3F_7{\cdot}ZnI$.

The decreased reactivity of the zinc relative to the magnesium compound is also shown by its failure to react with carbon dioxide, although it yielded 3 : 3 : 4 : 4 : 5 : 5 : 5-heptafluoropentan-2-one when treated with acetyl chloride. These isolated results indicate that the fluoroalkylzinc iodides cannot undergo addition to a carbonyl group, *i.e.*, if the yields can be improved the zinc compounds may be of value for the preparation of fluoro-ketones.

In the series R·MgI, R·ZnI, R·HgI, there is thus a much sharper change in reactivity from the magnesium compound to the zinc compound when R = perfluoroalkyl than when R = alkyl. The fluoroalkyl Grignard reagents appear to be less stable and more reactive (at least at low temperature) than the corresponding unsubstituted compounds, whereas the fluoroalkylzinc compounds resemble more the mercury compounds, which are less reactive towards functional groups.

Experimental

Heptafluoro-1-iodopropane, prepared from silver heptafluorobutyrate and iodine (Haszeldine, *J.*, 1951, 584; 1952, 4259), was dried over phosphoric oxide and stored in a vacuum. Reactions were carried out in conventional Grignard apparatus or in sealed tubes; moisture was excluded.

Reaction of Heptafluoroiodopropane with Zinc.—(a) *In dioxan.* Heptafluoroiodopropane (3·1 g.) and freshly prepared zinc powder (2·0 g.) were shaken with anhydrous dioxan (15 ml.) at 70° for 24 hr. The volatile products were 1*H*-heptafluoropropane (5%), b. p. −16° (Found: *M*, 170. Calc. for C_3HF_7: *M*, 170), and hexafluoropropene (2%), identified spectroscopically. Haszeldine (*J.*, 1952, 3423) reports b. p. −14° for heptafluoropropane. The unchanged heptafluoroiodopropane and solvent were pumped off and then distilled, to give unchanged heptafluoroiodopropane (*ca.* 20%) and perfluoro-*n*-hexane (15%), b. p. 54—57°. The pale yellow solid which remained after removal of the solvent contained heptafluoropropylzinc iodide (30%), estimated by reaction with hydrochloric acid or aqueous sodium hydroxide as described below.

The effect of temperature on the yields (%) is shown in the following Table:

Temp.	10°	30°	55°	82°	100°
C_3F_7H	0	5	4	7	10
C_3F_6	0	6	~3	10	13
C_6F_{14}	~3	11	21	33	45
$C_3F_7{\cdot}ZnI$	46	48	34	27	14

Hexafluoropropene and heptafluoropropane were separated by bromination or chlorination (cf. *J.*, 1952, 3423).

Heptafluoroiodopropane (8·0 g.), zinc (0·5 g.), and dioxan (3 ml.) reacted vigorously and exothermically after being left for 30 min. at 20°. After 12 hr., analysis of the brown solid product obtained by removal of the solvent, etc., *in vacuo* showed that it was mainly zinc iodide with <10% of heptafluoropropylzinc iodide.

(b) *In ethers.* Zinc (2·5 g.) and diethyl ether (35 ml.) were stirred at −10°, and heptafluoroiodopropane (5·0 g.), dissolved in diethyl ether (10 ml.), was added dropwise (1 hr.). The pale

brown mixture was stirred for 4 hr., then filtered, and the solvent and the unchanged heptafluoroiodopropane were removed *in vacuo*. The amount of unchanged heptafluoroiodopropane (38%) was calculated from the ultra-violet spectrum of the ethereal solution. The slightly coloured solid which remained was treated with an excess of aqueous sodium hydroxide, and from the heptafluoropropane evolved (see below) the yield of heptafluoropropylzinc iodide was calculated to be 53%. With a reaction time of 24 hr., the yields at −30°, 0°, 35°, and 70° (sealed tube) were 11, 56, 39, and 21%.

Similar yields were obtained by use of dibutyl ether as solvent.

(c) *In tetrahydropyran.* The experimental details of (b) were followed, with tetrahydropyran (25 ml. total) instead of diethyl ether. The yields of heptafluoropropylzinc iodide, heptafluoropropane, hexafluoropropene, and perfluorohexane at 0°, 20°, and 80° were 55, 0, 0, 5; 49, ~1, 5, 10; and 31, 8, 7, 19%.

(d) *No solvent.* Heptafluoroiodopropane (4·8 g.) and zinc (2·6 g.) were heated in a Carius tube at 165° (48 hr.), 190° (48 hr.), and 235° (48 hr.). Examination of the products at each stage revealed only small amounts of products with b. p. greater than that of heptafluoroiodopropane, and these did not contain zinc.

Heptafluoroiodopropane (6·0 g.) and zinc (2·6 g.), heated to 310° for 40 hr., gave unchanged iodide (4%) (Found: *M*, 296. Calc. for C_3F_7I: *M*, 296), perfluoro-*n*-hexane (*ca.* 60%), b. p. 55—58° (Found: *M*, 337. Calc. for C_6F_{14}: *M*, 338), and an unidentified fraction (0·7 g.), b. p. >58° (Found: *M*, 492), which did not contain zinc. The solid reaction products failed to liberate heptafluoropropane when treated with aqueous sodium hydroxide.

Isolation and Reactions of Heptafluoropropylzinc Iodide.—The experiment with dioxan at 30° [(a) above] was repeated. After reaction the solution was filtered and the solvent, etc., were removed at 20° *in vacuo*. The pale yellow residual solid was hygroscopic. It was dissolved in the minimum quantity of anhydrous dioxan and filtered, and light petroleum (b. p. 40—60°) was added dropwise until crystals appeared on cooling. These were filtered off at 5° in a dried atmosphere and transferred to a vacuum-desiccator (yield: 0·4 g., 11%). Samples were decomposed for analysis by fusion with sodium, by treatment with 15% aqueous sodium hydroxide, or by pyrolysis in oxygen over silver vanadate. The solid is *heptafluoropropylzinc iodide* containing one mol. of dioxan of solvation [Found: C, 18·1; H, 1·4; C_3F_7 (as C_3HF_7), 37·9; I, 28·8; Zn, 14·8. $C_7H_8O_2IF_7Zn$ requires C, 18·7; H, 1·8; C_3F_7, 37·6; I, 28·3; Zn, 14·5%].

Another sample of the solid was heated in a semimicro-sublimation apparatus at 10^{-4} mm. Dioxan was evolved at *ca.* 50°, and at *ca.* 60—75° a colourless microcrystalline solid sublimed. Fractions of this were taken, since zinc iodide tends to contaminate the product. A middle fraction was *heptafluoro*-n-*propylzinc iodide* [Found: C, 10·0; I, 35·5; C_3F_7 (as C_3HF_7), 46·2. C_3IF_7Zn requires C, 10·0; I, 35·2; C_3F_7, 46·8%]. At higher temperatures decomposition to volatile products, zinc iodide, and zinc fluoride occurred.

Unsolvated heptafluoropropylzinc iodide showed the following reactions:

A sample (0·19 g.) in a small platinum crucible was heated in a sealed Pyrex tube to 180—200°/760 mm. for 12 hr., to give hexafluoropropene (58%) (Found: *M*, 150. Calc. for C_3F_6: *M*, 150), identified by its infra-red spectrum, and a solid residue which contained zinc iodide and fluoride.

A sample (0·103 g.) heated at 100° with 15% aqueous sodium hydroxide (12 hr.) gave heptafluoropropane (99·5%) (Found: *M*, 170. Calc. for C_3HF_7: *M*, 170), identified spectroscopically.

A sample (0·094 g.) heated at 100° with water for 24 hr. gave heptafluoropropane (96·2%).

Anhydrous hydrogen chloride (100% excess) and heptafluoropropylzinc iodide (0·085 g.) were heated stepwise to 150° during 48 hr., to give heptafluoropropane (93%), identified spectroscopically.

The last reaction was repeated with chlorine and heptafluoropropylzinc iodide (0·089 g.); it gave 1-chloroheptafluoropropane (89%), b. p. −1° (isoteniscope) (Found: *M*, 203. Calc. for C_3ClF_7: *M*, 204·5). Haszeldine (*J.*, 1952, 4259) reports b. p. −1°.

Heptafluoropropylzinc iodide (1·3 g.), sealed in a Pyrex tube with acetyl chloride (30% excess) and heated stepwise to 130° (10 hr.), gave 3 : 3 : 4 : 4 : 5 : 5 : 5-heptafluoropentan-2-one (18%), b. p. 60° (isoteniscope) (Found: C, 28·4%; *M*, 210. Calc. for $C_5H_3OF_7$: C, 28·3%; *M*, 212). Haszeldine (*J.*, 1953, 1748) reports b. p. 58—59°. The formation of the tertiary alcohol could not be detected.

The following reactions were carried out with solutions of heptafluoropropylzinc iodide or with the solvated solid:

The solvated solid (0·2 g.), dissolved in ethanol (5 ml.) and heated to 120° for 5 hr., gave heptafluoropropane (71%), identified spectroscopically.

A solution of heptafluoropropylzinc iodide (0·2 g.) in dioxan (10 ml.) was shaken with an excess of carbon dioxide in a sealed tube (10 hr.) and then heated stepwise to 60° (8 hr.). Examination of the products after reaction with dilute sulphuric acid failed to reveal the presence of heptafluorobutyric acid (cf. *J.*, 1952, 3423).

Solutions of heptafluoropropylzinc iodide in ethyl ether, butyl ether, dioxan, or tetrahydropyran gave heptafluoropropane almost quantitatively when treated with 15% sodium hydroxide or 7N-sulphuric acid at 100° for 12 hr. Reaction with water was slow at 20°: after 2, 8, and 20 hr. the decomposition was 15, 63, and 81% respectively.

The authors thank the Minnesota Mining and Manufacturing Company for a gift of heptafluorobutyric acid, used in the later stages of this work. One of the authors (E. G. W.) thanks the British Council for the award of a British Council Scholarship for Germany, during the tenure of which this work was carried out.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, July 27th*, 1953]

---

725. *Properties of Periodate-oxidised Polysaccharides. Part I. The Preparation of Polymeric Substances containing Nitrogen from Oxidised Starches.*

By VINCENT C. BARRY and P. W. D. MITCHELL.

When *cyclo*hexylamine is added to an aqueous solution of periodate-oxidised starch, the double Schiff base of glyoxal separates. No such degradation takes place with *iso*nicotinoylhydrazine or thiosemicarbazide, or with a number of other reagents examined. With reagents of this kind, polymeric condensation products are formed. Some polymers formed from oxidised starch are described.

POLYSACCHARIDES containing α-glycol groups, after oxidation by periodate, can be degraded by treatment with phenylhydrazine (Barry, *Nature*, 1943, **152**, 537) and this process has been employed successfully in elucidating the fine structure of polysaccharides for which, in certain cases, the methylation procedure has proved ambiguous (Barry and Dillon, *Proc. Roy. Irish Acad.*, 1945, **50**, *B*, 349; Dillon and O'Colla, *ibid.*, 1951, **54**, *B*, 51; O'Colla, *ibid.*, **55**, *B*, 165, 321; Dillon, O'Ceallacháin, and O'Colla, *ibid.*, p. 331). Further studies have now been carried out in these laboratories on the properties of periodate-oxidised polysaccharides. In the first instance it has been shown that aqueous solutions of oxidised starch, on treatment in the cold with *cyclo*hexylamine, readily deposit the crystalline, double Schiff base of glyoxal, $(C_6H_{11}\cdot N{:}CH\cdot)_2$. Since *cyclo*hexylamine is a more stable reagent than phenylhydrazine and gives cleaner products it is possible that it may replace phenylhydrazine in the degradation mentioned above. This possibility is being examined. Simpler aliphatic bases, *e.g.*, ethylenediamine, bring about slow changes of the oxidised polysaccharide molecule without causing the separation of insoluble products.

In contrast to these degradative processes, however, we have now found that a large number and variety of other reagents condense with periodate-oxidised polysaccharides to form polymeric molecules. Readily isolatable polymers have been obtained on the addition, to aqueous solutions of oxidised starch, of *iso*nicotinoylhydrazine (isoniazid), thiosemicarbazide, *p*-aminobenzoic acid, the phenylenediamines, *p*-chloroaniline, etc. With hydrazine itself no precipitate is obtained until the solution is made faintly acid and then the solution sets to a tough colourless gel. The polymers formed from oxidised potato starch with isoniazid, thiosemicarbazide, and *p*-aminobenzoic acid are described in this paper.

The product (A), which separates when a dilute aqueous solution containing excess of isoniazid is added to an aqueous solution of periodate-oxidised starch can be obtained as a pale yellow amorphous powder, insoluble in water and in organic solvents, but soluble in ammonia and dilute alkali to pale yellow solutions. Decomposition takes place in these solutions and is particularly rapid in alkali and, if the alkaline solution is kept for a few

minutes and then acidified, the precipitate always contains crystalline material. (A) is also soluble in dilute mineral acid and in moderately dilute acetic acid. After thorough drying, it gives analyses fairly correct for the polymeric dialdehyde in which each modified hexose unit is combined with one molecule of isoniazid.

When an aqueous solution of thiosemicarbazide is used, a similar polymeric product (B) is obtained. This is a very pale yellow amorphous powder which proved on analysis to contain approximately one thiosemicarbazide residue for each α-glycol grouping in the original starch molecule. When thoroughly dried, it swells and dissolves gradually in dilute alkali to a pale yellow viscid solution which on acidification gives a flocculent colloidal precipitate. (B) does not dissolve in dilute ammonia or in 50% acetic acid. It is also insoluble in dilute mineral acid at ordinary temperatures; it dissolves on boiling but cannot be reprecipitated by neutralisation. The reduced solubility and increased stability of this polymer, as compared with (A), are probably due to the formation of cross-linkages. A similar stability was encountered in other polymers in which the formation of cross-linkages might be expected, *e.g.*, those formed from *o*-phenylenediamine and *p*-aminobenzaldehyde thiosemicarbazone.

In the preparation of the compound (C) from *p*-aminobenzoic acid and oxidised starch, an aqueous solution of the acid was at first used. The yellow material separating under these conditions contained much less nitrogen than expected. On the assumption that the polymer separated because of its insolubility when the condensation had proceeded only to a limited extent, the experiment was repeated with an aqueous solution of sodium *p*-aminobenzoate. The reaction mixture was kept for 24 hours and then made faintly acid with acetic acid. The resulting precipitate had a much higher nitrogen content and approximated more nearly to that required for one aminobenzoic acid residue per α-glycol group. On account of its content of free carboxyl groups, (C) dissolved readily in sodium hydrogen carbonate and in ammonia solutions.

The oxidised-starch solutions employed in these experiments were prepared in about 2% strength on the water-bath, complete dissolution being obtained in 1½—2 hours. If the solutions were boiled, there was considerable degradation, and polymer (A) prepared from such a solution proves on microscopic examination to be accompanied by crystalline material. The structure of these polymers is discussed in the following paper.

It is of interest that (A) and (B) are strongly inhibitory of the growth of *Mycobacterium tuberculosis in vitro*, and (A), in particular, is highly active in experimental mouse infections. Detailed biological results will be published elsewhere.

Experimental

Oxidised Starch.—Potato starch (4·5 g.), dried *in vacuo* over phosphoric oxide, was kept in the dark for 48 hr. with sodium metaperiodate (6·18 g. in 200 c.c. of water). The consumption of periodate corresponded to about 0·9 mol. per glucose anhydride unit. The oxidised starch was separated and washed with water until free from periodate and iodate, then washed with alcohol and ether, and dried in a vacuum-desiccator over concentrated sulphuric acid. The yield was quantitative. The oxidised starch may be dissolved by warming it on the water-bath for 1½—2 hr. with 50 parts of water.

Degradation with cyclo*Hexylamine.*—Oxidised starch solution (40 c.c.; 1%) was shaken with *cyclo*hexylamine (2 c.c.) for 24 hr. The mixture became milky immediately and colourless crystals separated gradually, accompanied by some gum. The Schiff base was separated and recrystallised twice from aqueous alcohol, giving colourless glistening leaflets (0·15 g.), m. p. 149—150°, undepressed on admixture with the crystalline product separating from a mixture of glyoxal and *cyclo*hexylamine (Found: C, 76·2; H, 10·8; N, 12·9. $C_{14}H_{24}N_2$ requires C, 76·4; H, 10·9; N, 12·7%).

Isoniazid Polymer (A).—An aqueous solution of oxidised starch (5 g.; 500 c.c.) was stirred with a solution of isoniazid (9 g. in 100 c.c. of water). It became milky and after 1 hr. the precipitate was coagulated by the addition of 1 c.c. of glacial acetic acid. The product was separated on a sintered-glass filter, washed well with water, alcohol, and ether, and dried in a vacuum-desiccator to a pale yellow powder (7·1 g.). After further drying *in vacuo* at 100° (P_2O_5), the *product* (Found: C, 47·8, 46·4; H, 5·3, 5·4; N, 15·4, 15·4. $C_{12}H_{13}N_3O_5,H_2O$ requires C, 48·5;

H, 5·0; N, 14·1%) had $[\alpha]_D^{23}$ + 122° (in 0·1N-NaOH; *c* 0·796) (22 min.) falling to +49·8° (100 min.).

Thiosemicarbazide Polymer (B).—An aqueous solution of thiosemicarbazide (6 g. in 200 c.c.) was added to oxidised starch solution (5 g. in 500 c.c.) with stirring and the mixture kept for 1 hr. The *product* (7·4 g.) was isolated, washed, and dried as above (Found: C, 32·7; H, 5·7; N, 17·9, 16·6; S, 14·2, 13·8. $C_7H_{11}O_4N_3S,H_2O$ requires C, 33·4; H, 5·2; N, 16·8; S, 12·8%) and had $[\alpha]_D^{21}$ + 104° (in 5% NaOH; *c* 0·781) (18 min.) falling to + 107° (72 min.).

p-*Aminobenzoic Acid Polymer* (C).—Oxidised starch solution (1 g. in 50 c.c.) was added to aqueous sodium *p*-aminobenzoate (2 g. in 50 c.c.) and the mixture kept overnight. The clear solution on acidification with dilute acetic acid gave a lemon-yellow gelatinous precipitate which was difficult to filter. It was separated and washed on the centrifuge, dissolved in alcohol, and reprecipitated by ether. In this condition it can be separated by filtration through a sintered-glass filter. It was obtained as a bright yellow powder which was dried in the vacuum-desiccator (H_2SO_4) and for 3 hr. at 100°/20 mm. (Found: C, 50·6; H, 5·6; N, 3·8. $C_{13}H_{13}O_6N,H_2O$ requires C, 52·5; H, 5·1; N, 4·7%). When dissolved in 0·1N-NaOH this *compound* showed negligible rotation. When the condensation was effected with aqueous *p*-aminobenzoic acid in place of its sodium salt, the product contained only 3·0% of nitrogen.

One of us (P. W. D. M.) is indebted to University College, Dublin, for the award of a Lasdon Foundation Research Fellowship.

Laboratories of the Medical Research Council of Ireland,
Trinity College, Dublin. [*Received, July 29th*, 1953.]

---

726. *The Isomerism of the Oximes. Part XLIV.* Alkylcinnamaldoximes, Aroylaldoximes, and the Action of Potassium Cyanide and Sodium Sulphite on Aldoximes and their O-Methyl Ethers.*

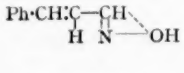
By M. Benger and O. L. Brady.

A number of α-alkylcinnamaldoximes have been studied; unlike the cinnamaldoxime and other substituted derivatives thereof these compounds could be obtained in only one form which probably has the α-configuration. Various aroyl derivatives of aldoximes have been prepared and their hydrolysis investigated.

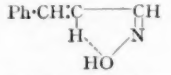
This communication deals with a variety of experimental observations to which reference will be made in subsequent papers but which did not, when first made, seem worthy of further development.

Cinnamaldehyde, unlike aldehydes in which the CHO group is attached directly to the benzene ring, on oximation in alkaline solution gives a mixture of the α- and β-isomerides in which the β-isomeride predominates (Bamberger and Goldschmidt, *Ber.*, 1894, **27**, 3429). On the other hand *o*-, *m*-, and *p*-nitro- and *o*-methoxy-cinnamaldehydes under these conditions give mainly the α-aldoximes (Brady and Thomas, *J.*, 1922, **121**, 2098; Brady and Grayson, *J.*, 1924, **125**, 1418).

It was thought that the behaviour of cinnamaldehyde was associated with the possibility in the cinnamaldoximes of a lone pair of electrons of the oxygen atom being associated with one or other of two methine-hydrogen atoms:



α-Cinnamaldoxime

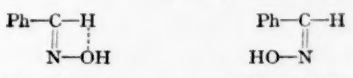


β-Cinnamaldoxime

Since the hydrogen bonding here implied is now generally regarded as an electrostatic effect the consideration of ring size is not critical but the influence of the lone pair of electrons of the oxygen in, for example, α-benzaldoxime will be small owing to the distance between the oxygen and the methine hydrogen yet, nevertheless, it may be enough, in

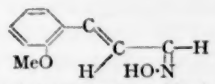
* Part XLIII, *J.*, 1950, 1243.

the absence of other possibilities of hydrogen bonding, to stabilise the α- relative to the β-isomeride. It will, at least, help to account for the fact that the α-aldoxime is a considerably stronger acid than the β-aldoxime.



α-Benzaldoxime

β-Benzaldoxime



β-*o*-Methoxycinnamaldoxime

This view will be developed in subsequent communications.

In the case of β-cinnamaldoxime the distance between the oxygen and the second methine-hydrogen atom can be less and consequently the β-isomeride is stabilised. In the nitrocinnamaldoximes the electron-withdrawing influence of the nitro-group will militate against hydrogen bonding, and in *o*-methoxycinnamaldoxime the oxygen of the methoxyl group can act as a competitor with the oximino-oxygen for the hydrogen bonding in the β-isomeride.

It is noteworthy that the ratio of the dissociation constants of the α- and the β-isomerides of benzaldoxime and of substituted benzaldoximes is about 4·5, whereas the ratio for α- and β-cinnamaldoximes is about 2·1 or much the same as that for α- and β-*p*-nitrobenzophenone oximes (Brady and Chokshi, *J.*, 1929, 946; Brady and Goldstein, *J.*, 1926, 1918). In the case of α- and β-benzaldoximes the higher dissociation constant of the α-isomeride indicates a lower electron density at its oxygen atom than at that of the β-isomeride, and this may be due to potential hydrogen bonding in the α-isomeride which is absent in the β-isomeride and in both α- and β-unsymmetrical benzophenoneoximes. The dissociation constants of α-benzaldoxime and α-cinnamaldoxime are about the same, but that of β-cinnamaldoxime is about three times that of β-benzaldoxime, which may be due to hydrogen bonding in the case of β-cinnamaldoxime.

In order to test this hypothesis the α-alkylcinnamaldoximes have been investigated as in their β-isomerides hydrogen bonding could not arise. Unfortunately the α-alkylcinnamic aldehydes on oximation gave one form of oxime only, and attempts to obtain the other isomeride by the usual methods were unsuccessful.

In the absence of the second isomeride one cannot decide with certainty the configuration of these compounds since the standard method depends on the relative ease of attack of OH^- on the methine-hydrogen atom or on the carbonyl group of the acetyl derivatives of the two isomerides, to give either nitrile or the original oximes; it does not, as often assumed, depend on an absolute difference in behaviour of the two isomerides (Hauser, Jordan, and O'Connor, *J. Amer. Chem. Soc.*, 1935, **57**, 2456; Benger and Brady, *J.*, 1950, 1221). For this reason the results give no certain support for our hypothesis, but the oximes behave more like α- than like β-aldoximes. For example, their acetyl derivatives on hydrolysis give mainly the original oxime; they give benzoyl derivatives which are hydrolysed to the original oxime instead of to the stereoisomeride (Brady and Thomas, *loc. cit.*; Brady and McHugh, *J.*, 1925, **127**, 2414); and α-methyl- and α-phenyl-cinnamaldoxime with 1-chloro-2 : 4-dinitrobenzene give dinitrophenyl ethers, but α-*n*-amylcinnamaldoxime resembles a β-oxime, giving dinitrophenol and α-*n*-amylcinnamaldehyde (Brady and Truszkowski, *J.*, 1924, **125**, 1087). On the other hand, the electron supply from the groups in the α-position may so stabilise the methine-hydrogen atom against removal by OH^- that even if the oximes have the β-configuration their acetyl derivatives may give but little nitrile on hydrolysis. Against this, however, is the fact that the acetyl derivatives of acetaldoxime and β-phenylpropaldoxime give mainly nitrile on alkaline hydrolysis.

Some approximate experiments have been performed on the relative amounts of oxime and nitrile formed in the alkaline hydrolysis of the acetyl derivatives, by determining the oxime formed by treatment with dinitrophenylhydrazine in ethanolic sulphuric acid (Brady and Peakin, *J.*, 1929, 478). The acetyl derivative of α-*n*-amylcinnamaldoxime gave 98% of oxime, of α-ethylcinnamaldoxime 71%, of α-phenylcinnamaldoxime 62%, of β-cinnamaldoxime 16%, of β-phenylpropaldoxime 19%, and of acetaldoxime 25%, on hydrolysis with ethanolic potassium hydroxide at room temperature.

Benger and Brady (*loc. cit.*) showed that, if the group attached to the oximino-oxygen atom was sufficiently electron-attracting, nitrile was obtained in appreciable quantities on alkaline hydrolysis at low temperatures even from the α-isomeride, *e.g.*, α-trichloroacetyl-*p*-nitrobenzaldoxime with 2N-sodium hydroxide at 0° gave 35% of nitrile. We have prepared the *o*-nitro-, *p*-nitro-, 3 : 5-dinitro-, and *p*-methoxy-benzoyl derivatives of a number of α-aldoximes and the phenylacetyl derivative of α-*p*-nitrobenzaldoxime to find out how far such substituents would favour nitrile formation on alkaline hydrolysis. At room temperature with ethanolic potassium hydroxide the *o*-nitrobenzoyl, *p*-nitrobenzoyl, and 3 : 5-dinitrobenzoyl derivatives of α-*o*-nitrobenzaldoxime gave mainly *o*-nitrobenzonitrile and a little α-*o*-nitrobenzaldoxime, but the α-*p*-methoxybenzoate gave mainly *o*-nitrobenzaldoxime and a little *o*-nitrobenzonitrile. These results are as expected, since the *o*-nitro-group greatly activates the methine-hydrogen atom, only *o*-nitro-substituted α-aldoximes are converted into nitriles by alkali, in other cases the oxime must be suitably acylated first (Reissert, *Ber.*, 1908, **41**, 3815; Brady and Goldstein, *J.*, 1926, 1918). The substituted benzoyl derivatives of other aldoximes regenerated the original oxime, as also did α-*p*-nitrobenzaldoxime phenylacetate.

Passerini (*Gazzetta*, 1926, **56**, 274) has stated that α- and β-*p*-methoxybenzaldoximes, among others, are converted into nitriles by boiling ethanolic potassium cyanide, but we have been unable to repeat his results with α-aldoximes except in the case of α-*o*-nitrobenzaldoxime.

The action of aqueous sodium sulphite on some α-aldoximes and their *O*-methyl ethers has also been investigated. When the aldoxime contained a nitro-group in the *o*-position amides were obtained, but not in other cases. It is probable that these amides were formed through the nitrile, as it has been found that benzonitrile and nitrobenzonitriles give amides more or less readily in boiling aqueous sodium sulphite but that such compounds as *p*-methoxy- and 3 : 4-methylenedioxy-benzonitrile do not do so even after 8 hours' boiling.

The action of sodium sulphite on *O*-methyl ethers is interesting. α-*O*-Methyl-*o*-nitro- and α-*O*-methyl-3 : 4-methylenedioxy-6-nitro-benzaldoxime gave good yields of the amide, but α-*o*-methoxy-*O*-methyl- and α-*O*-methyl-3 : 4-methylenedioxy-benzaldoxime were unaffected. α-*O*-Methyl-*p*-nitrobenzaldoxime yielded a considerable amount of α-*p*-nitrobenzaldoxime, and α-*O*-methyl-*m*-nitrobenzaldoxime a small amount of α-*m*-nitrobenzaldoxime. It seems probable therefore that the sodium sulphite surprisingly acts in the first instance as a demethylating agent to *O*-methyl ethers of oximes containing a nitro-group, and that, if the nitro-group is in the *o*-position, the resulting oxime is converted, as before, into the amide.

Experimental

α-*Alkylcinnamaldoximes* *.—α-Methyl-, α-ethyl-, α-*n*-amyl-, and α-phenyl-cinnamaldehydes were prepared by a Claisen condensation of benzaldehyde with propaldehyde, *n*-butyraldehyde, heptaldehyde, and phenylacetaldehyde respectively. α-*Phenylcinnamaldehyde* formed colourless plates (from ethanol), m. p. 95°, b. p. 208°/16 mm. (Found: C, 86·1; H, 5·8. $C_{15}H_{12}O$ requires C, 86·5; H, 5·8%). The following were prepared by the action of dinitrophenylhydrazine sulphate in ethanol: α-*methylcinnamaldehyde* 2 : 4-*dinitrophenylhydrazone*, red plates (from benzene), m. p. 208° (Found: C, 58·6; H, 4·2. $C_{16}H_{14}O_4N_4$ requires C, 58·9; H, 4·0%); α-ethylcinnamaldehyde 2 : 4-dinitrophenylhydrazone, dark red prisms (from benzene), m. p. 188°; α-n-*amylcinnamaldehyde* 2 : 4-*dinitrophenylhydrazone*, red plates (from benzene), m. p. 168° (Found: C, 62·0; H, 5·8. $C_{20}H_{22}O_4N_4$ requires C, 62·8; H, 5·7%); and α-*phenylcinnamaldehyde* 2 : 4-*dinitrophenylhydrazone*, vermilion prisms (from xylene), m. p. 239° (Found: C, 64·4; H, 4·1. $C_{21}H_{16}O_4N_4$ requires C, 64·9; H, 4·1%).

The oximes were prepared by mixing an ethanolic solution of 1 mol. of the aldehyde with ethanolic solutions of 1½ mols. each of hydroxylamine hydrochloride and sodium hydroxide. After a few minutes' warming the clear solution was decanted from the precipitated sodium chloride into a large volume of dilute hydrochloric acid, and the precipitated oxime collected, washed with water, and crystallised. Thus were obtained: α-*methylcinnamaldoxime*,* silky

* In all cases the α indicates the position of the alkyl group and not the configuration of the aldoxime.

needles (from ethanol), m. p. 130° (Found: C, 73·8; H, 6·8. $C_{10}H_{11}ON$ requires C, 74·4; H, 6·8%); *α-ethylcinnamaldoxime*, stout needles (from light petroleum), m. p. 103° (Found: C, 75·4; H, 7·4. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·4%); α-n-*amylcinnamaldoxime*, plates (from light petroleum), m. p. 70° (Found: C, 77·7; H, 8·6. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·8%); and *α-phenylcinnamaldoxime*, prisms (from ethanol), m. p. 165° (Found: C, 80·9; H, 5·6. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8%).

α-Methylcinnamaldoxime was acetylated by the standard method, giving an uncrystallisable oil which on hydrolysis with alcoholic 0·5N-potassium hydroxide regenerated the original oxime in good yield. As the oxime is insoluble in 2N-alkali it was dissolved in 4 times its weight of cold benzoyl chloride, kept for 1 hr., and shaken with a large excess of 2N-sodium carbonate. Crystallising the precipitate from benzene gave *α-methylcinnamaldoxime benzoate* in colourless prisms, m. p. 77° (Found: C, 77·1; H, 5·7. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·6%). Hydrolysis with alcoholic potassium hydroxide regenerated the original oxime. Ethanolic solutions of equimolecular amounts of the oxime, 1-chloro-2 : 4-dinitrobenzene, and sodium were mixed and warmed; O-2 : 4-*dinitrophenyl-α-methylcinnamaldoxime* separated slowly and crystallised from benzene in very pale greenish-yellow needles, m. p. 162° (Found: C, 58·5; H, 3·7. $C_{16}H_{13}O_5N_3$ requires C, 58·7; H, 4·0%). A solution of the oxime is dry ether, on saturation with hydrogen chloride, gave α-methylcinnamaldoxime hydrochloride as a bright yellow powder, m. p. 145°, which with 2N-sodium carbonate regenerated the original oxime.

α-*n*-Amylcinnamaldoxime, acetylated by the standard method, gave its *acetate* as colourless needles (from benzene), m. p. 37° (Found: C, 73·9; H, 8·0. $C_{16}H_{21}O_2N$ requires C, 74·1; H, 8·1%). Alkaline hydrolysis of this compound gave a good yield of the original oxime. Its *benzoate*, prepared as above, separated as an oil which crystallised after 10 weeks in a desiccator as colourless needles, m. p. 36°, but could not be recrystallised (Found: C, 79·8; H, 7·2. $C_{21}H_{23}O_2N$ requires C, 78·5; H, 7·2%). Alkaline hydrolysis regenerated the original oxime. α-*n*-Amylcinnamaldoxime hydrochloride, m. p. 82°, was formed as a white precipitate by passing hydrogen chloride into a dry ethereal solution of the oxime and regenerated the original oxime with 2N-sodium carbonate. When α-*n*-amylcinnamaldoxime was treated with 1-chloro-2 : 4-dinitrobenzene and sodium ethoxide in ethanol, only sodium dinitrophenoxide and α-*n*-amylcinnamaldehyde, identified after steam-distillation as its dinitrophenylhydrazone, could be isolated. α-*n*-Amylcinnamaldoxime (10 g.) was boiled under reflux with acetic anhydride (25 c.c.) for 2 hr., excess of anhydride removed with 2N-sodium carbonate, and the oil extracted with ether and distilled under reduced pressure; α-n-*amylcinnamonitrile* was obtained as a yellow liquid, b. p. 174—176°/16 mm. (Found: C, 83·9; H, 8·6. $C_{14}H_{17}N$ requires C, 83·9; H, 8·5%). On hydrolysis with ethanolic potassium hydroxide it gave α-n-*amylcinnamic acid*, colourless needles (from ethanol), m. p. 118° (Found: C, 77·3; H, 8·6. $C_{14}H_{18}O_2$ requires C, 77·1; H, 8·3%).

α-Phenylcinnamaldoxime, treated as above, gave its *acetate* as colourless crystals (from ethanol), m. p. 105° (Found: C, 76·7; H, 5·5. $C_{12}H_{15}O_2N$ requires C, 77·0; H, 5·7%), which on alkaline hydrolysis gave the original oxime; and the 2 : 4-*dinitrophenyl ether* as pale yellow needles (from acetone), m. p. 194° (Found: C, 64·3; H, 4·0. $C_{21}H_{15}O_5N_3$ requires C, 64·8; H, 3·9%). A solution of the oxime in ether gave no precipitate with hydrogen chloride; evaporating the ether in a current of dry air gave a yellow gum which effervesced with sodium carbonate and gave the original oxime.

Solutions of the above oximes in benzene were exposed in a quartz vessel to ultra-violet light for 72 hr., but no indication of isomerisation was observed (cf. Brady and McHugh, *J.*, 1924, **125**, 547).

Quantitative Hydrolysis of Acetyl Derivatives.—A weighed quantity of the oxime was dissolved at 20° in about double of the amount of pure acetic anhydride required to acetylate it, then kept for 5 min., and the solution was added to twice the amount of ethanolic 2N-potassium hydroxide required to neutralise the total acetic anhydride employed; this avoided the troublesome isolation of liquid acetyl derivatives (cf. Benger and Brady, *J.*, 1950, 1221). The solution was kept for 1 hr. with occasional shaking and acidified with dilute sulphuric acid, the potassium sulphate which crystallised removed, and a slight excess of an ethanolic solution of 2 : 4-dinitrophenylhydrazine sulphate added. The solution was warmed, then kept for 2 hr., and the precipitated dinitrophenylhydrazone collected, washed with a little ethanol, then with water, dried, and weighed. In the case of acetaldoxime, since acetonitrile is miscible with water, and acetaldehyde dinitrophenylhydrazone is appreciably soluble in alcohol, a dilute solution of 2 : 4-dinitrophenylhydrazine hydrochloride in 2N-hydrochloric acid was used instead of the sulphate. The results are recorded above.

Substituted Benzoyl Derivatives of Substituted Benzaldoximes.—The *products* listed in the Table were prepared by shaking a solution of the oxime in excess of 2N-sodium hydroxide with a solution of a slight excess of the appropriate acid chloride dissolved in the minimum amount of ether or chloroform, the mixture being kept alkaline throughout the reaction; as the products were sparingly soluble in ether or chloroform they could be collected by filtration.

α-p-*Nitrobenzaldoxime O-phenylacetate* was prepared by treating α-*p*-nitrobenzaldoxime (3 g.) with a solution of phenylacetic anhydride (8 g.) in the minimum of dry ether at room temperature. After 1 hr. the ether was removed by a current of air, and the oily residue shaken with 2N-sodium carbonate, and the solid obtained crystallised from benzene–light petroleum as colourless plates, m. p. 109° (Found: C, 63·0; H, 4·2. $C_{15}H_{12}O_4N_2$ requires C, 63·4; H, 4·2%).

The acyl derivatives (1 g. each) were hydrolysed by being kept for 12 hr. at room temperature with ethanolic 0·5N-potassium hydroxide (60 c.c.), and the mixtures were poured into a slight excess of saturated ammonium chloride solution. Most of the alcohol was removed on the water-bath, and the product examined for oxime, nitrile, or amide. *o*-Nitrobenzaldoxime *o*- and *p*-nitro- and 3 : 5-dinitro-benzoate gave mainly *o*-nitrobenzonitrile and a little α-*o*-nitrobenzaldoxime, whereas the *p*-anisoate gave mainly α-*o*-nitrobenzaldoxime and a little *o*-nitrobenzonitrile. The other compounds gave the corresponding α-aldoxime, except *p*-dimethylaminobenzaldoxime 3 : 5-dinitrobenzoate which yielded only a tar.

Substituted α-O-*acylbenzaldoximes*, Ar·CH:N·OAr'.

Substituents in Ar	Ar'	M. p.	Solvent for crystn.*	Found (%) C	Found (%) H	Formula	Reqd. (%) C	Reqd. (%) H
o-NO_2	*o*-NO_2	142°	AcOH	53·3	2·7	$C_{14}H_9O_6N_3$	53·3	2·9
,,	*p*-NO_2	178	,,	53·3	2·8	,,	,,	,,
,,	3 : 5-$(NO_2)_2$	184	,,	46·5	2·3	$C_{14}H_8O_8N_4$	46·6	2·2
,,	*p*-MeO	125	,,	60·2	4·0	$C_{15}H_{12}O_5N_2$	60·0	4·0
p-NO_2	*p*-NO_2	193	,, [a]	53·2	3·0	$C_{14}H_9O_6N_3$	53·3	2·9
,,	*o*-NO_2	178	,, [b]	53·3	2·9	,,	,,	,,
,,	3 : 5-$(NO_2)_2$	180	,, [a, b]	46·5	2·4	$C_{14}H_8O_8N_4$	46·6	2·2
,,	*p*-MeO	179	EtOH [c]	60·2	4·0	$C_{15}H_{12}O_5N_2$	60·0	4·0
p-MeO	*p*-NO_2	164	,, [d]	60·2	4·0	,,	,,	,,
,,	*p*-MeO	150	C_6H_6	67·4	5·3	$C_{16}H_{15}O_4N$	67·4	5·3
3 : 4-$(MeO)_2$	*p*-NO_2	178	$COMe_2$ [e]	57·2	3·2	$C_{15}H_{10}O_6N_2$	57·3	3·2
,,	*o*-NO_2	128	EtOH	57·5	3·4	,,	,,	,,
,,	3 : 5-$(NO_2)_2$	193	$COMe_2$–EtOH [f]	50·0	2·7	$C_{15}H_8O_8N_2$	50·1	2·5
,,	*p*-MeO	188	C_6H_6	64·4	4·4	$C_{16}H_{13}O_5N_3$	64·2	4·4
p-NMe_2	*o*-NO_2	122	C_6H_6–Pet [e, g]	61·6	4·7	$C_{16}H_{15}O_4N_3$	61·4	4·8
,,	*p*-NO_2	170	C_6H_6–EtOAc [h]	61·5	4·8	,,	,,	,,
,,	3 : 5-$(NO_2)_2$	151	EtOAc [i]	53·6	3·8	$C_{16}H_{14}O_6N_4$	53·6	3·9

* Colourless needles unless otherwise stated. Pet. = light petroleum.

[a] Leaflets. [b] Buff. [c] Plates. [d] Pale yellow. [e] Canary-yellow. [f] Cadmium-yellow. [g] Orange plates. [h] Vermilion prisms. [i] Scarlet.

Action of Aqueous Potassium Cyanide and Sodium Sulphite on Aldoximes and their O-*Methyl Ethers.*—The oxime (5 g.) and potassium cyanide (3 g.) were heated under reflux for 3 hr. in ethanol, and most of the solvent was removed on the water-bath. The remaining solution was treated with excess of 2N-sodium hydroxide, to convert unchanged oxime into sodium salt, and extracted with ether. The extract was examined for nitrile, and the aqueous layer acidified for recovery of oxime. With α-*m*-nitro-, α-*p*-nitro-, α-*o*-methoxy-, α-*p*-methoxy-, α-3 : 4-methylenedioxy-, and α-3 : 4-methylenedioxy-6-nitro-benzaldoxime most of the oxime was recovered unchanged and no nitrile could be detected.

When α-*o*-nitrobenzaldoxime (5 g.) was heated with ethanolic potassium cyanide as above and the solution evaporated to small bulk, 3 g. of *o*-nitrobenzonitrile crystallised.

The *O*-methyl ether (5 g.) and potassium cyanide (3 g.) were heated under reflux for 5 hr. in ethanol, and most of the solvent was removed; with α-*O*-methyl-*o*-nitrobenzaldoxime, *o*-nitrobenzamide (2 g.) crystallised, but with α-*O*-methyl-*p*-nitro-, α-*O*-methyl-*m*-nitro-, α-*O*-methyl-3 : 4-methylenedioxy-6-nitro-, and α-*p*-methoxy-*o*-methyl-benzaldoximes unchanged *O*-ether was recovered in good yield.

The oxime (5 g.) was boiled with water (250 c.c.) and sodium sulphite (5 g.) for various times, evaporated to small bulk, and cooled. α-*o*-Nitrobenzaldoxime boiled for 1 hr. gave almost pure *o*-nitrobenzamide (3·5 g.); α-*p*-nitro-, α-3 : 4-methylenedioxy-, α-4-methoxy-3-nitro-, and α-*o*-methoxy-benzaldoxime gave unchanged oxime after 7 hr.' boiling; α-3 : 4-

methylenedioxy-6-nitrobenzaldoxime was boiled for 6 hr., a deep red solution being obtained, which was evaporated to dryness and extracted with boiling ethanol; the solid which separated on cooling was crystallised again from alcohol, giving 3 : 4-*methylenedioxy-6-nitrobenzamide* in buff-coloured needles, m. p. 198° (Found: C, 45·9; H, 2·9. $C_8H_6O_5N_2$ requires C, 45·7; H, 2·9%). Mixed with the oxime (m. p. 203°) it melted at 161°. Similarly treated α-3 : 4-dimethoxy-6-nitrobenzaldoxime gave 3 : 4-*dimethoxy-6-nitrobenzamide*, yellow needles (from benzene), m. p. 184° (Found: C, 47·6; H, 4·5. $C_9H_{10}O_5N_2$ requires C, 47·8; H, 4·4%).

α-*O*-Methyl-*o*-nitrobenzaldoxime (5 g.) was boiled with sodium sulphite (5 g.) and water (200 c.c.) for 20 min., all the ether dissolving; on evaporation to small bulk and cooling, *o*-nitrobenzamide (3·5 g.) crystallised. Similarly, α-3 : 4-dimethoxy-*O*-methyl-6-nitrobenzaldoxime after 2 hr.' boiling gave the amide, but the *O*-methyl ethers of α-3 : 4-methylenedioxy- and α-*o*-methoxy-benzaldoxime were recovered unchanged after such treatment. α-*O*-Methyl-*p*-nitrobenzaldoxime dissolved to a red solution after 6 hr.' boiling; evaporation to dryness gave a red solid from which no amide could be extracted, but addition of hydrochloric acid yielded α-*p*-nitrobenzaldoxime; similarly, α-*O*-methyl-*m*-nitrobenzaldoxime gave a small amount of α-*m*-nitrobenzaldoxime.

Action of Sodium Sulphite on Nitriles.—The nitrile (1 g.) was boiled with sodium sulphite (1 g.) in water (150 c.c.), and the solution evaporated to small bulk and cooled. *o*- and *p*-Nitrobenzonitrile gave the amides after 30 min.' boiling, *m*-nitrobenzonitrile after 90 min.' boiling, and benzonitrile after 8 hr.' boiling, but *p*-methoxy- and 3 : 4-methylenedioxy-benzonitrile gave no amide after 8 hr.' boiling.

THE WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES,
UNIVERSITY COLLEGE, LONDON, W.C.1.

[*Received, June 12th,* 1953.]

---

727. *Some Properties of Selenium Tetrafluoride.*

By R. D. PEACOCK.

The vapour pressure and surface tension of selenium tetrafluoride have been determined. Reactions of the compound have been further investigated, and those with mercury and some oxides and oxy-compounds of both metals and non-metals are described.

IN a recent paper (Aynsley, Peacock, and Robinson, *J.*, 1952, 1231) the preparation of selenium tetrafluoride was described and values for the density and melting and boiling points were given. Only one approximate value for the surface tension was obtained; this and also the vapour pressure have now been measured over a range of temperatures. As previously indicated, selenium tetrafluoride is remarkable in its chemical behaviour and exhibits unexpected compound formation and solvent properties towards a number of substances

The vapour pressure can be conveniently measured by what is essentially the isoteniscope method. The logarithm of the vapour pressure gave a straight line when plotted against the reciprocal of the absolute temperature except for below 20°. Between that temperature and 70° the vapour pressures are given by the equation $\log P = 9{\cdot}44 - 2457/T$ (where T = temperature in °K), from which the boiling point found by extrapolation is 101·6° (cf. 106° experimentally determined). A latent heat of vaporisation of 11,240 cal. per mole, and a Trouton's constant of 30·0 can be deduced. If the relation $T_{B.p.}/T_c = 0{\cdot}6$ is assumed to apply, the critical temperature is approximately 290°.

The surface tension referred to above had been obtained by observing capillary rise. This method is not satisfactory because the liquid does not readily wet glass, and a method based on the measurement of maximum bubble pressure was used instead. Between −10° and 100° the surface tension is given by the equation $\gamma = 38{\cdot}40 - 0{\cdot}124t$ dynes/cm., where t = temperature in °C. Extrapolation to the boiling point gives $\gamma = 25{\cdot}80$ dynes/cm., and further extrapolation to zero surface tension suggests a critical temperature of 310°, which is of the same order as that deduced above from vapour-pressure data.

A further examination of the reaction of selenium tetrafluoride with mercury shows that the attack is slow at 20° but much more rapid at the boiling point and can be completed

by refluxing. The white solid formed, $HgSeF_4$, is slightly soluble in selenium tetrafluoride. On addition of water, the solid evolves heat but does not suffer very obvious change, though some of it goes into solution since the liquid becomes acid and gives a white precipitate with potassium chloride. Alkali causes the compound to blacken immediately, leading to precipitation of the element, and cold concentrated hydrochloric acid turns it a reddish colour which becomes grey and metallic-looking when the liquid in which it is suspended is boiled.

Of the solvent properties of selenium tetrafluoride, the most striking is its ready dissolution of brown vanadium pentoxide to give a colourless solution of considerable concentration from which white crystalline plates of $VOF_3,2SeF_4$ [probably the salt $(SeF_3)_2VOF_5$ (cf. K_2VOF_5)] separate on cooling. Even titanium dioxide and tantalum pentoxide dissolve in the tetrafluoride.

Sulphur trioxide reacts with much heat and, after removal of the excess of selenium tetrafluoride in a vacuum, yields an oily liquid, SeF_4,SO_3, which on cooling solidifies to colourless crystals, m. p. 70°. In the absence of solid the compound readily supercools to room temperature; it may be distilled at about 170° in a vacuum without decomposition. With water, it reacts violently giving among other things fluorosulphonic acid. Again the material most probably has the character of a salt $(SeF_3)SO_3F$.

The vigorous reaction with potassium permanganate is interesting. The green solution first formed almost immediately becomes reddish-brown, evolves oxygen, and deposits a red-brown solid, $KMnF_5$. The reaction is probably represented by $4KMnO_4 + 10SeF_4 \longrightarrow 4KMnF_5 + 10SeOF_2 + 3O_2$.

The reaction with selenium dioxide provides the most convenient method of preparing selenium oxyfluoride yet described. Excess of dioxide is used and the product is fractionated.

When first prepared in this laboratory the tetrafluoride was believed, on visual evidence, not to attack glass; it has since been shown to do so, though quite slowly and even when completely free from hydrogen fluoride. The attack on a borosilicate is surprising. At room temperature silicon tetrafluoride and boron trifluoride are produced in readily measurable pressures after a week, and the inner surface of the glass above the liquid becomes slowly covered with a white deposit of selenium dioxide. The reaction may be represented by $SiO_2 + SeF_4 \longrightarrow SiF_4 + SeO_2$, and correspondingly for boron. These facts do not prevent this compound from being usefully handled in glass since it can be satisfactorily separated from these materials by distillation.

Experimental

Preparation of Selenium Tetrafluoride.—Selenium was allowed to react at 0° with fluorine by the method described by Aynsley, Peacock, and Robinson (*loc. cit.*), which allows of the convenient preparation of up to 300 g. of the tetrafluoride at one time.

Vapour Pressure.—Freshly distilled material, purified in a vacuum, was carefully degassed several times by alternate freezing and melting in a high vacuum. The sample was degassed frequently during the measurements. At low temperatures the vapour pressure was read directly by means of a cathetometer on the isoteniscope which was charged with selenium tetrafluoride. Pressures were converted into mm. of mercury. At higher temperatures the isoteniscope was used as a null instrument through air pressure to a mercury manometer.

Temp.	−11·1°	−5·0°	0°	10·3°	19·8°	25·6°	29·6°	34·5°	40·1°	47·7°	60·0°	69·0°
V. p. (mm.)	0·71	1·31	2·50	5·77	12·02	16·42	21·26	29·11	41·20	61·90	114·5	187·4

Surface Tension.—A suitable modification of the maximum bubble pressure method was used. The Pyrex instrument was calibrated before and after the determination, water being used as the reference liquid.

Temp.	−7·6°	5·0°	17·8°	29·0°	39·6°	50·3°	60·9°	71·8°	77·8°	82·0°	89·2°
γ (dynes/cm.)	39·06	38·21	36·33	34·99	33·30	31·97	30·89	29·20	28·80	28·20	27·51

Reactions.—(a) *With mercury.* Mercury, carefully purified and dried, was refluxed with a large excess of selenium tetrafluoride for 30 hr. The white residual *compound* was dried in a vacuum at 20° (Found: Hg, 57·3; Se, 21·8; F, 20·7%; equiv., 348·4. $HgSeF_4$ requires Hg, 56·4; Se, 22·4; F, 21·2%; equiv., 355·6).

(b) *With vanadium pentoxide.* Vanadium pentoxide was dissolved in warm selenium tetrafluoride, and the solution allowed to cool. The excess of tetrafluoride was removed in a vacuum at 20°, leaving the *salt* (Found: V, 11·5; Se, 35·6; F, 47·9. $VOF_3,2SeF_4$ requires V, 11·7; Se, 36·4; F, 48·2%).

(c) *With sulphur trioxide.* Sulphur trioxide was allowed to react with a large excess of selenium tetrafluoride. The excess of reagent was carefully pumped off, the temperature being raised slowly from 20° to 160°, above which the *compound* itself began to distil (Found: SO_3, 34·0; Se, 33·4; F, 32·0. SO_3,SeF_4 requires SO_3, 34·1; Se, 33·6; F, 32·3%).

(d) *With potassium permanganate.* Selenium tetrafluoride was condensed on to a small quantity of solid potassium permanganate. When the frothing had subsided the mixture was refluxed for a short time for completion of the reaction. The excess of solvent was removed in a vacuum at 20°, and the last traces pumped off from the *fluoromanganate* at 160° (Found: Mn, 29·3; F, 49·8. $KMnF_6$ requires Mn, 29·1; F, 50·3%).

(e) *With glass.* About 30 c.c. of selenium tetrafluoride in an evacuated Pyrex system provided with a manometer were kept for several weeks at room temperature. The pressure of gas, which after about a week was 2—3 mm., increased uniformly to 30 cm. after 6 months. After some time a white incrustation began to show on the glass, and a few white crystals appeared in the liquid; analysis showed these to be mainly selenium dioxide. At the end of the experiment the gases were condensed by means of liquid oxygen and proved to be a mixture of silicon tetrafluoride and boron trifluoride.

I am indebted to Dr. P. L. Robinson for experimental facilities and advice and to Mr. J. Smith for practical assistance. The cell used was lent by Imperial Chemical Industries Limited.

INORGANIC CHEMISTRY LABORATORIES,
KING'S COLLEGE, NEWCASTLE-ON-TYNE. [*Received, June 15th,* 1953.]

---

728. *Alkyl–Oxygen Fission in Carboxylic Esters. Part XII.** 1-o-*Methoxyphenylethyl and* α-*Naphthylphenylmethyl Compounds. The Relative Effects of the Introduction of* o- *and of* p-*Methoxyl Groups into Phenylmethyl Compounds.*

By R. E. DABBY, A. G. DAVIES, J. KENYON, and B. J. LYONS.

1-*o*-Methoxyphenylethyl alcohol has been resolved *via* its hydrogen phthalate, and the tendency of this ester and of α-naphthylphenylmethyl hydrogen phthalate to undergo alkyl–oxygen fission has been investigated. It is shown that an *o*-methoxyl group is somewhat less effective than a *p*-methoxyl group in promoting alkyl–oxygen fission in 1-phenylethyl hydrogen phthalate, and in diphenylmethyl and α-naphthylphenylmethyl compounds. This is ascribed to the super-position upon the powerful, activating, electron-repelling, mesomeric effect of the methoxyl group ($+M$, $CH_3—\overset{\curvearrowright}{O}—$), of a weaker, deactivating, electron-attracting, inductive effect ($-I$, $CH_3—O\leftarrow$) which becomes attentuated on relay through the carbon–carbon bonds of the benzene ring.

1-*o*-METHOXYPHENYLETHYL ALCOHOL has been resolved by fractional crystallisation of the brucine salt of its hydrogen phthalate, and the tendency of this ester to undergo alkyl–oxygen fission has been investigated. 1-*o*-Methoxyphenylethyl hydrogen phthalate undergoes unimolecular alkyl–oxygen fission reactions according to the equation:

$$R—\overset{\curvearrowright}{O}\cdot CO\cdot C_6H_4\cdot CO_2H \underset{}{\overset{\text{Slow}}{\rightleftharpoons}} C_6H_4(CO_2H)_2 + R^+ \xrightarrow[Y]{\text{Fast}} RY$$

(where R = *o*-MeO·C_6H_4·CHMe; Y = HO^-, AcOH, etc., *p*-Me·C_6H_4·SO_2^-, MeOH, and $RO_2C\cdot C_6H_4\cdot CO_2^-$) more readily than 1-phenylethyl hydrogen phthalate (Part II, *J.*, 1942, 605, and Part III, *J.*, 1946, 797), but less readily than 1-*p*-methoxyphenylethyl hydrogen

* Part XI, *J.*, 1952, 4964.

phthalate. A parallel difference exists between the diphenylmethyl (Parts II and III, *locc. cit.*) and *o*- and *p*-methoxydiphenylmethyl compounds.

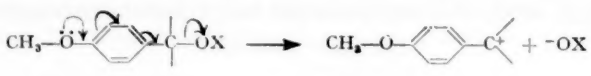
Attempts to resolve α-naphthylphenylmethanol *via* the alkaloidal salts of its hydrogen phthalate and hydrogen succinate were unsuccessful. The tendency of this alcohol and its hydrogen phthalate to undergo typical alkyl–oxygen fission reactions (formation of bis-ether, and of chloride, from the alcohol; formation of *p*-tolyl sulphone, ethyl ether, and neutral phthalate, from the hydrogen phthalate) has been investigated, and again it is shown that the reactivity of related structures by such a mechanism follows the sequence : α-naphthylphenylmethyl < *o*-methoxyphenyl-α-naphthylmethyl < *p*-methoxyphenyl-α-naphthylmethyl compounds.

These differences between the compounds carrying *o*- and *p*-methoxyl substituents, are summarised in the Table.

Reaction	Reacting molecule: *o*-$MeO\cdot C_6H_4\cdot CHMe\cdot O\cdot CO\cdot C_6H_4\cdot CO_2H$	Reacting molecule: *p*-Isomer *
Hydrolysis	Optical purity of alcohol produced.	
(i) In 8% aq. NaOH	99%	90%
(ii) In 4% aq. NaOH	95%	Much racemisation
Racemisation	Half-life of racemisation at room temp.	
(i) In acetic acid	63 hr.	9 hr.
(ii) In 2N-formic acid in acetic acid	55 hr.	7 hr.
(iii) In 5N-formic acid in acetic acid	43 hr.	2·5 hr.
(iv) In 2·5N-HCl in acetone	50 min.	Approx. 1·5 min.
Reaction with sodium toluene-*p*-sulphinate in 0·3N-NaOH	Almost quant. yield of sulphone after 1 month.	Quant. yield of sulphone after 5 days.
Reaction with MeOH.	No reaction with anhyd. MeOH. (−)-Ester gives (±)-methyl ether after 5 hr. in 90% aqueous MeOH at b. p.	(−)-Ester gives (±)-methyl ether after 12 hr. in anhydrous MeOH at room temp.
Formation of neutral ester	Neutral ester obtained from 0·1N-NaOH after 5 days.	Neutral ester obtained from 0·3N-NaOH after 2 days.
	o-$MeO\cdot C_6H_4\cdot CHPhX$ †	*p*-Isomer †
Reaction with MeOH (X = OH).	No reaction on distillation with MeOH during 6 hr.	Methyl ether formed.
Reaction with sodium toluene-*p*-sulphinate in 0·3N-NaOH (X = *o*-$HO_2C\cdot C_6H_4\cdot CO_2^-$).	Pptn. of sulphone starts after 3 hr.; complete after 6 days.	Quant. yield of sulphone after 20 min.
	o-$MeO\cdot C_6H_4\cdot CH(C_{10}H_7\text{-}1)\cdot O\cdot CO\cdot C_6H_4\cdot CO_2H$ ‡	*p*-Isomer ‡
Formation of neutral ester from 0·3N-NaOH.	Good yield after 4 days.	Good yield after 2 days.

* Part IV, *J.*, 1946, 803; K. A. Nandi, Thesis, London, 1940.
† Part II (*loc. cit.*); R. Poplett, Thesis, London, 1944.
‡ Part III (*loc. cit.*); A. A. Evans, Thesis, London, 1944.

Thus the introduction of an *o*- or *p*-methoxyl group into the benzene ring of such 1-phenylmethyl compounds increases their tendency to react by a unimolecular alkyl–oxygen fission mechanism, and this effect is greater when the methoxyl group is located in the *para*- than when it is in the *ortho*-position. This overall accelerating effect, which has also been observed in di-*p*-methoxyphenylmethanol (Part X, *J.*, 1951, 386; Balfe, Kenyon, and Thain, *J.*, 1952, 790) and in 2 : 4 : 6-trimethoxyphenylmethyl compounds (Part XI, *J.*, 1952, 4964), may be ascribed to the powerful, mesomeric, electron release (+*M* effect) of the methoxyl group operating in conjugation with the alkyl–oxygen bond, *e.g.* :



Some further factor must account for the reduced effectiveness of the methoxyl group when located in the *ortho*-position. Steric inhibition of resonance by the methoxyl group in the 1-*o*-methoxyphenylethyl cation cannot be of major importance in this respect since molecular models show that the ion can assume a strainless planar configuration. More probably the effect is a result of the superposition of the inductive electron attraction ($-I$ effect, $CH_3—O\leftarrow$) of the methoxyl group upon its more powerful mesomeric electron release; this inductive effect rapidly becomes attenuated on relay through carbon–carbon bonds, and thus will operate more effectively from the *ortho*- than from the *para*-position in decreasing the electron releasing power of the " alkyl " carbon atom, and hence in reducing its tendency to undergo alkyl–oxygen fission.

Experimental

(±)-1-o-*Methoxyphenylethyl Alcohol.*—The alcohol, prepared from methylmagnesium iodide and *o*-methoxybenzaldehyde in 86% yield, had b. p. 84—86°/0·6 mm., n_D^{25} 1·5372. Klages (*Ber.*, 1903, **36**, 3588) reports $n_D^{14·7}$ 1·5379. The phenylurethane had m. p. 105—106°; Klages (*loc. cit.*) reports 106°. *Di*-(1-o-*methoxyphenylethyl*) *ether* was formed (1%) when the alcohol was distilled at 124—126°/17 mm., or, very slowly, when the pure alcohol was kept at room temperature; it separates from methanol as needles, m. p. 117—118° (Found: C, 75·3; H, 7·6. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·7%).

(±)-1-o-*Methoxyphenylethyl Hydrogen Phthalate.*—A solution of the alcohol (52 g.) and phthalic anhydride (53 g.) in pyridine (28 g.) was kept at 60° for 2 hr. and, next day, decomposed with ice and dilute hydrochloric acid. The resulting *ester* separated slowly from carbon disulphide–ligroin in large rectangular prisms, m. p. 93—94° (90%) (Found, by titration: equiv., 297. $C_{17}H_{16}O_5$ requires equiv., 300).

(+)-1-o-*Methoxyphenylethyl Hydrogen Phthalate.*—From a solution of the (±)-ester (36 g.) and brucine (54 g.) in acetone (250 c.c.), the brucine salt of the (+)-ester rapidly separated. After four recrystallisations from acetone–chloroform (1 : 1), it (needles, m. p. 193—194°; 35 g.) was suspended in acetone and decomposed by dilute hydrochloric acid, and the liberated ester extracted with ether. The (+)-hydrogen *ester*, a clear viscous oil, had equiv. 299 (by titration) and $[\alpha]_D^{19}$ +19·30° (*l*, 2; *c*, 2·081 in $CHCl_3$).

(−)-1-o-*Methoxyphenylethyl Hydrogen Phthalate.*—The mother-liquor from the first crop of brucine salt was concentrated and set aside; the brucine salt of the (−)-ester (35 g.) slowly separated. This salt, after eight recrystallisations from acetone, was obtained as needles, m. p. 112—114° (18 g.), which, after decomposition with dilute hydrochloric acid yielded the (−)-hydrogen ester as an oil, $[\alpha]_D^{18}$ −19·2° (*l*, 2; *c*, 1·545 in $CHCl_3$).

(−)-1-o-*Methoxyphenylethyl Alcohol.*—The (+)-hydrogen phthalate (3 g.) in a solution of sodium (1 g.) in 96% ethanol (20 c.c.) was heated on the steam-bath for some minutes until a thick precipitate was produced. The mixture, diluted with water and extracted with ether, yielded the (−)-alcohol (1·2 g.), b. p. 83—85°/0·5 mm., n_D^{25} 1·5310, d_4^{25} 1·0780, $[\alpha]_D^{20}$ −50·1° (homogeneous, l, 0·25) [Klages, *loc. cit.*, gives $d_4^{14·7}$ 1·0862 for the (±)-alcohol]. This (−)-alcohol was reconverted into the hydrogen phthalate, $[\alpha]_D^{21}$ +19·15° (*l*, 2; *c*, 1·931 in $CHCl_3$).

(±)-, (+)-, *and* (−)-1-o-*Methoxyphenylethyl Benzoate.*—From the (±)-alcohol (1·5 g.), benzoyl chloride (1·4 g.), and pyridine (1·0 g.), the (±)-*benzoate* was obtained as needles (from ethanol), m. p. 34—36° (Found: C, 75·5; H, 6·2. $C_{16}H_{16}O_3$ requires C, 75·4; H, 6·2%). By a similar procedure the (−)-alcohol yielded the (+)-benzoate, m. p. 45—46°, $[\alpha]_D^{19}$ +81·2° (*l*, 1; *c*, 1·405 in $CHCl_3$), and the (+)-alcohol yielded the (−)-benzoate, m. p. 45—46°, $[\alpha]_D^{20}$ −80·6° (l, 1; *c*, 1·402 in $CHCl_3$).

Reactions of 1-o-*Methoxyphenylethyl Hydrogen Phthalate.*—(i) *Hydrolysis with dilute aqueous sodium hydroxide.* The optical purity of the alcohol produced by hydrolysis with 8% and with 4% aqueous sodium hydroxide is reported in the Table.

(ii) *Racemisation in acid solution.* The half-life of the racemisation of the hydrogen phthalate under acid conditions at room temperature, is given in the Table. From an acetic acid solution of the (+)-hydrogen phthalate, the (±)-acetate was isolated: the rotatory power of a solution of the (+)-hydrogen phthalate (1·0 g.) in glacial acetic acid (20 c.c.) at room temperature fell to 50% of the original value after 63 hr. and to 10% after 3 weeks. The mixture yielded, on decomposition, the (±)-acetate (0·4 g.), b. p. 118—120°/17 mm., n_D^{25} 1·5267.

(iii) *Formation of* 1-o-*methoxyphenylethyl* p-*tolyl sulphone.* From a mixture of the (−)-hydrogen phthalate (0·6 g.) in aqueous sodium hydroxide (7·0 c.c. of 0·3N) and sodium toluene-*p*-sulphinate (0·43 g.) in water (3 c.c.), deposition of a white solid began after 2 days and was

complete after 1 month. Recrystallisation from ethanol gave (±)-1-o-*methoxyphenylethyl* p-*tolyl sulphone* (0·45 g.) as short rods, m. p. 131—132° (Found: C, 66·0; H, 6·2; S, 10·9. $C_{16}H_{18}O_3S$ requires C, 66·2; H, 6·2; S, 11·0%). At 70° the reaction was complete after 15 min. The same sulphone was obtained by the oxidation of the corresponding sulphide. From a mixture of the (±)-hydrogen phthalate (7·5 g.) in acetone (20 c.c.) and thio-*p*-cresol (3·0 g.) suspended in 98% formic acid (15 c.c.), phthalic acid (3·6 g.) rapidly separated. The filtrate was neutralised with dilute sodium hydroxide solution and extracted with ether, yielding 1-o-*methoxyphenylethyl* p-*tolyl sulphide* (6·0 g.), b. p. 183—185°/17 mm. (Found: C, 74·6; H, 7·1; S, 12·3. $C_{16}H_{18}OS$ requires C, 74·4; H, 7·0; S, 12·4%). Hydrogen peroxide (6·0 c.c. of 90-vol.) was added to a solution of the sulphide (2·0 g.) in glacial acetic acid (20 c.c.); after 2 days the solution was diluted with aqueous sodium hydroxide solution, yielding 1-*o*-methoxyphenylethyl *p*-tolyl sulphone (2·0 g.), m. p. and mixed m. p. 131—133°.

(iv) *Formation of* 1-o-*methoxyphenylethyl methyl ether.* A solution of the (−)-hydrogen phthalate (2·5 g.) and water (2·0 g.) in methanol (25 c.c.) was boiled under reflux for 2 hr., whereafter the solution possessed 4% of its original rotatory power. After a further 3 hr. the optically inactive mixture yielded the (±)-*methyl ether* (1·0 g.), b. p. 90—93°/17 mm., n_D^{25} 1·5973 (Found: C, 72·4; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·6%). No reaction occurred when a similar anhydrous reaction mixture was heated under reflux for 6 hr.

(v) *Formation of neutral ester.* After 24 hr., a solution of the (+)-hydrogen phthalate (6 g.) in aqueous sodium hydroxide (200 c.c. of 0·1N) began to deposit the oily *di*-(1-o-*methoxyphenylethyl*) *phthalate*. After 5 days this was removed and heated at 100°/0·4 mm. to remove traces of the alcohol, leaving a residual oil which could not be solidified, $[\alpha]_D^{20}$ +4·5° (*l*, 2; *c*, 4·00 in $CHCl_3$) (Found by hydrolysis: equiv., 420. $C_{26}H_{26}O_6$ requires equiv., 434). Hydrolysis of this neutral ester with alcoholic sodium hydroxide gave (−)-1-*o*-methoxyphenylethyl alcohol, b. p. 83—85°/0·5 mm., $[\alpha]_D^{20}$ −15·4° (*l*, 0·25; homogeneous), n_D^{25} 1·5340. Hydrolysis of the original (+)-hydrogen phthalate under similar conditions yielded the optically pure alcohol.

(−)-1-p-*Methoxyphenylethyl Hydrogen Phthalate.*—This ester was prepared and resolved as described in Part IV (*loc. cit.*). The half-life of racemisation under acid conditions is reported in the Table.

α-*Naphthylphenylmethanol.*—The alcohol, prepared in good yield either by the interaction of α-naphthylmagnesium bromide and benzaldehyde, or by the reduction of α-naphthyl phenyl ketone in ethanol with zinc dust and sodium hydroxide, separates from carbon disulphide in needles, m. p. 86° (Acree, *Ber.*, 1904, **37**, 2727, gives m. p. 85—86°). Its solution in pyridine is readily converted by acetic anhydride or acetyl chloride into the corresponding *acetate*, needles, m. p. 80—80·5° (Found: C, 82·5; H, 5·9. $C_{19}H_{16}O_2$ requires C, 81·9; H, 6·0%). After 35 hr. at 150—155°, the alcohol (3·0 g.) yielded *di*-(α-*naphthylphenylmethyl*) *ether* (0·30 g.) as white glistening needles (from acetone), m. p. 172—173° (Found: C, 90·0; H, 5·7. $C_{34}H_{26}O$ requires C, 90·1; H, 5·8%).

α-*Naphthylphenylmethyl Hydrogen Phthalate.*—A mixture of the alcohol (23·5 g.), phthalic anhydride (14·8 g.), and pyridine (15 c.c.) was kept at 55—60° for 16 hr. and the resulting homogeneous liquid, diluted with an equal volume of acetone, was decomposed with cold hydrochloric acid. The initially pasty *hydrogen phthalate* rapidly hardened (m. p. 153—154°) and separated from methanol in prismatic needles, m. p. 158—158·5° (36·5 g.) (Found, by titration: equiv., 384. $C_{25}H_{18}O_4$ requires equiv., 382).

α-*Naphthylphenylmethyl Hydrogen Succinate.*—A mixture of the alcohol (7 g.), succinic anhydride (3 g.), and pyridine (5 c.c.), after 4 hr. on the steam-bath, yielded the *hydrogen succinate* (9·7 g.) as short needles, m. p. 122—123° (Found: equiv., 338. $C_{21}H_{18}O_4$ requires equiv., 334).

Each of these acid esters was combined with several of the commoner alkaloids but in all cases the salts remained non-crystalline, and no optical resolution could be accomplished.

Formation of α-*Naphthylphenylmethyl Chloride.*—(i) *With thionyl chloride.* Thionyl chloride (7·0 c.c.) was added slowly to a solution of the alcohol (9·0 g.) in benzene (50 c.c.). After being heated under reflux for 1 hr., the mixture was decolorised with animal charcoal, and the solvent removed, yielding α-naphthylphenylmethyl chloride (7·0 g.) as needles (from ether–light petroleum), m. p. 59° (Found: Cl, 13·5. Calc. for $C_{17}H_{13}Cl$: Cl, 14·0%). Norris and Blake (*J. Amer. Chem. Soc.*, 1928, **50**, 1812) give m. p. 64—64·5°.

(ii) *With hydrochloric acid.* A mixture of the alcohol (12·0 g.) in acetone (15 c.c.) and concentrated hydrochloric acid (100 c.c.) was kept for 30 min. at 80°. The resulting oil was dried *in vacuo* (KOH), and extracted with light petroleum, the extract yielding the chloride (from ligroin or carbon disulphide, 9·0 g.), b. p. 230°/17 mm., m. p. and mixed m. p. 59°.

(iii) *With acetyl chloride.* Acetyl chloride (2·0 c.c.) was added to the alcohol (2·0 g.) at room temperature, an orange colour immediately developing. After drying *in vacuo* (KOH), the mixture yielded the chloride (from ligroin, 1·2 g.), b. p. 228°/16 mm., m. p. and mixed m. p. 59°.

Reactions of α-Naphthylphenylethyl Hydrogen Phthalate.—(i) *Formation of α-naphthylphenylmethyl p-tolyl sulphone.* A solution of the hydrogen phthalate (4·0 g.) and sodium toluene-*p*-sulphinate (2·25 g.) in 98% formic acid (50 c.c.) was heated on the steam-bath for 8 hr. and diluted with water. The resulting *sulphone* (3·3 g.) separated from ethanol in plates, m. p. 122° (Found: S, 8·3. $C_{24}H_{20}O_2S$ requires S, 8·5%). On the other hand, from an aqueous sodium hydroxide solution of the acid phthalic ester and sodium toluene-*p*-sulphinate, the only product which separated was the alcohol.

(ii) *Formation of ethyl α-naphthylphenylmethyl ether.* A solution of the hydrogen phthalate (5·0 g.) in absolute ethanol (75 c.c.) was heated under reflux for 18 hr. The products consisted of unchanged acid ester (2·2 g.) and the *ethyl ether*, b. p. 202—204°/14 mm., which separated from ether–light petroleum in needles (1·6 g.), m. p. 47° (Found: C, 87·2; H, 7·1. $C_{19}H_{18}O$ requires C, 87·0; H, 6·9%). Replacement of absolute ethanol by 70% ethanol resulted in an improvement of the yield of ethyl ether from 46% to 58% during the same period of heating.

The ethyl ether was also obtained in quantitative yield when α-naphthylphenylmethyl chloride was heated with absolute ethanol under reflux for 3 hr.

(iii) *Non-formation of neutral phthalic or succinic esters.* Solutions of the acid phthalic or succinic esters in equivalent amounts of aqueous sodium hydroxide of different concentrations (N/20—N) deposited—very slowly at room temperature, more rapidly on warming—α-naphthylphenylmethanol quantitatively. There was no trace of a neutral ester. Similarly, a solution of the acid phthalic ester (2·0 g.) in chloroform (20 c.c.) after being heated under reflux for 30 hr. yielded the unchanged acid ester (1·95 g.).

Thanks are expressed to Imperial Chemical Industries Limited for a grant.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, June 16th,* 1953.]

---

729. *The Preparation of o-Aminophenyl Sulphates.*

By E. BOYLAND, D. MANSON, and PETER SIMS.

Methods for the synthesis of a number of *o*-aminophenyl sulphate derivatives are described. The oxidation of aromatic amines with persulphate in alkaline solution yields *ortho*-substituted derivatives, and the reaction is a convenient method of preparation of *o*-aminophenyl sulphates.

THE metabolism of aromatic amines in animals normally leads to the production of aminophenols and acetamidophenols, which are usually excreted in conjugated forms as the sulphuric esters or glucuronides. Usually the hydroxyl group is introduced in the *para*-position with respect to the amino-group, and in the *ortho*-position if the *para*-position is blocked. In some cases, however, hydroxylation in the *ortho*-position occurs when the *para*-position is free; *e.g.*, dimethylaniline, when given to dogs, is excreted as *o*-aminophenyl hydrogen sulphate (Horn, *Z. physiol. Chem.* 1936, **238**, 84; **242**, 23). 2-Naphthylamine is excreted mainly as 2-amino-1-naphthyl hydrogen sulphate in dogs (Wiley, *J. Biol. Chem.*, 1938, **124**, 627), in which species 2-naphthylamine produces cancer of the bladder, and mainly as 6-amino-2-naphthol derivatives in rats and rabbits (Dobriner, Hoffman, and Rhoads, *Science*, 1941, **93**, 600; Manson and Young, *Biochem. J.*, 1950, **47**, 170) in which it does not induce bladder cancer. Some *o*-aminophenols, *e.g.*, 2-amino-1-naphthol (Hueper, *Arch. Path.*, 1938, **25**, 856), 3 : 3'-dihydroxybenzidine (Baker, *Acta Un. int. Cancer*, 1950, **7**, 46), and 1-amino-2-naphthol (Bonser, Clayson, and Jull, in the press) have been shown to be carcinogenic. Investigation of the metabolism of aromatic amines necessitated the preparation of aminophenyl esters for comparison, and for the study of chemical oxidation which might resemble biological oxidation.

The preparation of 2-amino-1-naphthyl hydrogen sulphate from the corresponding aminophenol and chlorosulphonic acid as described by Wiley (*loc. cit.*), gave very small yields, but it was readily prepared by (1) treatment of the 2-phthaloylamino-1-naphthol

with chlorosulphonic acid and removal of the phthaloyl group with acetic acid, (2) reduction of 2-nitro-1-naphthyl hydrogen sulphate, and (3) oxidation of 2-naphthylamine with persulphate in alkaline solution. The last method is new, and seems to be of general application.

In studying the reaction of phenols with chlorosulphonic acid, Burkhardt and Lapworth (*J.*, 1926, 684) found that the order of addition of the reagents affected the yield. When *o*-aminophenol was treated with chlorosulphonic acid in dimethylaniline (without carbon disulphide), potassium 2-hydroxyphenylsulphamate, *o*-HO·C_6H_4·NH·SO_3K, was the main product, and *o*-aminophenyl hydrogen sulphate could not be detected.

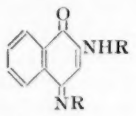
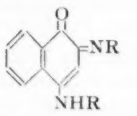
Burkhardt and Wood (*J.*, 1929, 141) prepared many aminoaryl hydrogen sulphates by reduction of the corresponding nitro-derivatives with ferrous hydroxide, and we have now prepared 2-amino-1-naphthyl hydrogen sulphate by this method. Catalytic reduction of the nitro-group has also been employed (Bernstein and McGilvery, *J. Biol. Chem.*, 1952, **198**, 195). Attempted preparation of 2-nitro-1-naphthyl sulphate by heating 2-nitro-1-naphthol with potassium pyrosulphate in dimethylaniline was unsuccessful. The use of carbon disulphide as a diluent is probably not necessary, and 1-nitro-2-naphthyl potassium sulphate described by Burkhardt and Wood (*loc. cit.*) has been prepared by using pyridine as the solvent (cf. Feigenbaum and Neuberg, *J. Amer. Chem. Soc.*, 1941, **63**, 3529).

It seemed probable that aminoaryl hydrogen sulphates could be prepared more readily from the aminophenols if the amino-groups were protected. 2-Phthaloylamino-1-naphthol was treated with chlorosulphonic acid, but the sulphuric ester fraction obtained failed to give 2-amino-1-naphthyl hydrogen sulphate with hydrazine. Treatment of the sulphuric ester with dilute acetic acid, which caused little hydrolysis of the sulphate group, gave 2-amino-1-naphthyl hydrogen sulphate in low yield. This method could not be applied to the synthesis of *o*-aminophenyl hydrogen sulphate because here too hydrazine was without effect, and acetic acid caused hydrolysis of the sulphate.

The oxidation with persulphate is of interest as it provides a new and easy route for the preparation of some *o*-aminophenols, and it is in many ways different from the Elbs persulphate oxidation. The reaction is remarkable in that it yields only *o*-aminophenols, in which it resembles that process of biological oxidation which appears to be associated with carcinogenesis.

Although the sulphate of 3 : 3′-dihydroxybenzidine could not be isolated from the persulphate oxidation of benzidine, treatment of aniline with persulphate yielded *o*-aminophenyl potassium sulphate, which resembled the product obtained by Burkhardt and Wood (*loc. cit.*) by reduction of 2-nitrophenyl potassium sulphate. The free acid was not precipitated when a saturated solution of the salt was treated with mineral acid (*p*-aminophenyl hydrogen sulphate is precipitated under these conditions; Burkhardt *et al.*, *loc. cit.*); the *N*-acetyl derivative of the potassium salt was readily obtained. Hydrolysis with hot mineral acid afforded *o*-aminophenol. A neutral amorphous product obtained in this oxidation was apparently a mixture, but the constituents could not be identified.

Dimethylaniline, under similar conditions, afforded *o*-dimethylaminophenyl potassium sulphate, which, when treated with cold mineral acid, gave *o*-dimethylaminophenyl hydrogen sulphate. This was hydrolysed by hot mineral acid to *o*-dimethylaminophenol. 1-Naphthylamine was oxidised to 1-amino-2-naphthyl potassium sulphate from a solution of which (contrary to a statement by Burkhardt *et al.*, *loc. cit.*) the free acid separated on acidification. Hydrolysis with hot mineral acid yielded 1-amino-2-naphthol.

(I)   (II)

Oxidation of 2-naphthylamine with persulphate afforded crude 2-amino-1-naphthyl hydrogen sulphate which was best purified by crystallisation of the sodium or potassium salt. Hydrolysis with hot dilute acid yielded 2-amino-1-naphthol. The neutral by-product from the oxidation was examined in detail for comparison with the products

obtained on use of benzoyl peroxide (to be discussed in a later paper). Chromatography of the benzene-soluble fraction (the benzene-insoluble fraction was a brown amorphous substance) showed the presence of 1 : 2-5 : 6-dibenzophenazine, 2-2′-naphthylamino-1 : 4-naphthaquinone 4-2′-naphthylimide (I; R = 2-$C_{10}H_7$) [or possibly the isomer (II; R = 2-$C_{10}H_7$)], and a small amount of an unidentified red substance of m. p. 279°. The imide (I or II; R = 2-$C_{10}H_7$) has previously been prepared by Meldola (*J.*, 1884, 156) by the action of 2 : 4-dibromo-1-naphthol on 2-naphthylamine. The isomer (I or II; R = 1-$C_{10}H_7$) has been prepared by the condensation of 1-naphthylamine with 2-nitroso-1-naphthol (Fischer and Hepp, *Annalen*, 1893, **272**, 306), and aniline gives similarly (I or II; R = Ph) (Bromme, *Ber.*, 1888, **21**, 391). The imide (I or II; R = 2-$C_{10}H_7$), m. p. 246—247°, was prepared in a similar manner by the condensation of 2-naphthylamine with 2-nitroso-1-naphthol and was identical with the imide, m. p. 252—253°, obtained from the persulphate oxidation. 1 : 2-5 : 6-Dibenzophenazine is a product of the oxidation of 2-naphthylamine with lead dioxide (Clemo and Dawson, *J.*, 1939, 1114) or ferric chloride.

The fact that, with simple aromatic amines, substitution apparently occurs only in the *ortho*-position relative to the amino-group suggests that a special mechanism may be functioning. In the oxidation of phenols with persulphate, where a free radical, the sulphate-ion radical, is thought to be responsible (Baker and Brown, *J.*, 1948, 2303), substitution normally takes place in the *para*-position, and *ortho*-substitution occurs only when the *para*-position is blocked. In the latter case yields are much reduced. With 1- and 2-naphthol, substitution occurs in the 4- and the 1-position respectively (Desai and Sethna, *J. Indian Chem. Soc.*, 1951, **28**, 213). Both the hydroxyl and the amino-group have similar orientating effects on further aromatic substitution, so that *para*-substituted aromatic amines might be expected as a result of persulphate oxidation. It is suggested, therefore, that, in these cases, there is addition to the 1 : 2-double bond, followed by elimination of a potassium hydrogen sulphate residue. In 2-naphthylamine, where, by this mechanism, addition across the 1 : 2- or the 2 : 3-bond is equally possible, addition to the 1 : 2-bond takes place because of its more unsaturated nature. The action of persulphate on nuclear-substituted aromatic amines is under investigation.

Experimental

Oxidation of Aniline.—Aniline (5 g.), in water (500 ml.) and 2N-potassium hydroxide (50 ml.), was treated at room temperature with potassium persulphate (14·5 g.) in saturated aqueous solution, added during 8 hr. with continuous stirring. The mixture was kept overnight and the precipitate (2·9 g.) collected. The filtrate was evaporated to 100 ml. under reduced pressure, washed with ether (3 × 100 ml.), and made acid to Congo-red with 2N-sulphuric acid. The filtered solution was extracted with butanol (6 × 100 ml.), slight excess of aqueous 2N-potassium hydroxide was added, and the butanol extract evaporated to dryness under reduced pressure. The residue was extracted with hot 95% aqueous ethanol (4 × 100 ml.), and the combined extracts were evaporated to 25 ml. and kept at 0° for some hours. *o*-Aminophenyl potassium sulphate (1·9 g., 15·5%*) was obtained, separating from 90% ethanol containing a trace of aqueous potassium hydroxide as light brown plates (Found: N, 6·3; K, 17·6. Calc. for $C_6H_6O_4NSK$: N, 6·2; K, 17·2%).

The N-*acetyl* derivative of the potassium salt separated from 80% ethanol as needles (Found: N, 5·1. $C_8H_8O_5NSK$ requires N, 5·2%).

Hydrolysis of the potassium salt (500 mg.) with concentrated hydrochloric acid (2 ml.) at 100° for 30 min. and partial neutralisation with 2N-potassium hydroxide afforded *o*-aminophenol (245 mg., 90%), separating from water containing a trace of sodium hydrogen sulphite as needles, m. p. and mixed m. p. 173—174° (Found: N, 12·6. Calc. for C_6H_7ON: N, 12·8%). The dibenzoyl derivative crystallised from ethanol as needles, m. p. and mixed m. p. 182—183° (Found: N, 4·4. Calc. for $C_{20}H_{15}O_3N$: N, 4·4%).

Oxidation of Dimethylaniline.—Dimethylaniline (5 g.) in water (250 ml.), acetone (400 ml.), and 2N-potassium hydroxide (30 ml.) was treated with potassium persulphate (11·2 g.) as before. The solution was evaporated to 250 ml., washed with ether (3 × 150 ml.), and evaporated to

* In the persulphate oxidations, yields are calculated on the amount of persulphate used. Unoxidised amines were present in the reaction mixtures from all these oxidations, but use of excess of persulphate generally resulted in more complex products.

dryness under reduced pressure, and the residue extracted with hot 95% ethanol (3 × 50 ml.). The combined extracts were diluted with ether (1·5 l.); *o-dimethylaminophenyl potassium sulphate* (4·2 g., 40%) was obtained, separating from 95% ethanol as elongated plates (Found: N, 5·2; K, 15·6. $C_8H_{10}O_4NSK$ requires N, 5·5; K, 15·3%).

The potassium salt (0·46 g.) in water (2 ml.) and hydrochloric acid (2 ml.) afforded *o-dimethylaminophenyl hydrogen sulphate* (310 mg., 82%), prisms (from aqueous ethanol), m. p. 217—219° (decomp.) (Found: C, 44·3; H, 5·3; N, 6·1; S, 15·0. $C_8H_{11}O_4NS$ requires C, 44·2; H, 5·1; N, 6·45; S, 14·8%).

When the acid (0·4 g.) was heated at 100° with concentrated hydrochloric acid (5 ml.) for 1 hr. and the ice-cold solution partially neutralized with 2N-sodium hydroxide, *o*-dimethylaminophenol (210 mg., 83%) separated as needles, m. p. and mixed m. p. 44—45°, raised to 46° by crystallisation from aqueous ethanol.

Oxidation of 1-Naphthylamine.—1-Naphthylamine (5 g.) in water (600 ml.), pyridine (200 ml.), and 2N-potassium hydroxide (36 ml.) was treated with potassium persulphate (9·5 g.) as before. The mixture was evaporated to 100 ml. under reduced pressure, unchanged 1-naphthylamine separated, and the cooled solution washed with ether (2 × 100 ml.). The solution was kept at 0° overnight, 1-amino-2-naphthyl potassium sulphate separating. The filtrate was acidified to Congo-red with 2N-sulphuric acid, and the solution filtered and extracted with butanol (6 × 100 ml.). The extract was dried (Na_2SO_4), treated with slight excess of 2N-potassium hydroxide, and evaporated under reduced pressure. Crystallisation of the residue from 90% ethanol gave more of the potassium salt. 1-Amino-2-naphthyl potassium sulphate (1·7 g., 17·5%) crystallised from 90% ethanol as hexagonal plates (Found: S, 12·0; K, 13·8. Calc. for $C_{10}H_8O_4NSK$: S, 11·6; K, 14·1%). The *sodium* salt (prepared in a similar manner with sodium persulphate) separated from 90% ethanol as hexagonal plates (Found: S, 12·8. $C_{10}H_8O_4NSNa$ requires S, 12·3%). Treatment of a saturated solution of the potassium or sodium salt with concentrated hydrochloric acid produced *1-amino-2-naphthyl hydrogen sulphate*, separating from water as prismatic needles, decomp. 203—204° (Found: S, 13·3 $C_{10}H_9O_4NS$ requires S, 13·4%). Aqueous and aqueous-alcoholic solutions of the sodium and potassium salts had a faint blue fluorescence in daylight and the acid and salts had a bright blue fluorescence in ultra-violet light.

The acid (0·5 g.) was heated to 100° with concentrated hydrochloric acid (2 ml.) for 30 min. 1-Amino-2-naphthol hydrochloride (0·35 g.) separated from the cooled solution. The dibenzoyl derivative crystallised from ethanol as needles, m. p. and mixed m. p. 225—226° (Found: N, 3·9. Calc. for $C_{24}H_{17}O_3N$: N, 3·8%), and the diacetyl derivative from ethanol as leaflets, m. p. and mixed m. p. 202—203° (Found: N, 5·9. Calc. for $C_{14}H_{13}O_3N$: N, 5·8%).

2-Amino-1-naphthyl Hydrogen Sulphate.—(*a*) 2-Nitro-1-naphthol (9·7 g.) (Burkhardt and Wood, *loc. cit.*) was added to chlorosulphonic acid (8·4 g.) in dry dimethylaniline (40 ml.) and carbon disulphide (40 ml.) as described by Burkhardt and Lapworth (*loc. cit.*). After 3 days, the mixture was poured into 6% aqueous potassium hydroxide (200 ml.). The solution was filtered, and the filtrate was washed with benzene and acidified at 0°. 2-Nitro-1-naphthol was separated, and the inorganic sulphate was removed from the filtrate with a slight excess of potassium hydroxide and barium chloride at 50°. The solution was concentrated; at 0° potassium 2-nitro-1-naphthyl sulphate (5·7 g.) separated in pale yellow needles, contaminated with red crystals of potassium 2-nitro-1-naphthoxide. Aqueous potassium 2-nitro-1-naphthyl sulphate (5·7 g.) was added during 1 hr., with stirring, to hydrated ferrous sulphate (47·5 g.) and barium carbonate (45 g.) in water (200 ml.) at 70°. After 2 hr., the solution was filtered hot, made alkaline with aqueous potassium hydroxide, and concentrated under reduced pressure. Ethanol (4 vols.) was added, and the solution was treated with charcoal. Acidification of the cold filtrate with concentrated hydrochloric acid yielded the ester (1·5 g.) as prisms, m. p. 224—225° (decomp.) (Found: N, 5·8; S, 13·2. Calc. for $C_{10}H_9O_4NS$: N, 5·9; S, 13·4%).

(*b*) 2-Amino-1-naphthol hydrochloride (2·8 g.) in pyridine (15 ml.) was added to chlorosulphonic acid (1·9 g.) in dry dimethylaniline (10 ml.) and carbon disulphide (50 ml.) at 0°. Next day, the mixture was poured into 7·5% aqueous potassium hydroxide (100 ml.), and the solution was washed with benzene. When the solution was concentrated under reduced pressure and acidified, a violet precipitate (0·8 g.), m. p. 200—210°, was obtained, which was precipitated (4 times) with acid from aqueous-ethanolic potassium hydroxide (charcoal), to give the ester (0·2 g., 6%), m. p. 223—225° (decomp.), undepressed in admixture with material from (*a*).

(*c*) Via *2-phthaloylamino-1-naphthol.* When 2-amino-1-naphthol hydrochloride (5·0 g.), phthalic anhydride (7·6 g.), and anhydrous sodium acetate (2·1 g.) in glacial acetic acid (250 ml.) were heated under reflux for 2 hr., and the solution allowed to cool, *2-phthaloylamino-1-naphthol*

(5·2 g., 79%), m. p. 268—269°, separated (Found: N, 5·2. $C_{18}H_{11}O_3N$ requires N, 4·8%). The derivative was soluble in dilute sodium hydroxide and gave a red colour with diazotised sulphanilic acid.

Chlorosulphonic acid (2·3 g.) was added to pyridine (30 ml.) with cooling, followed by 2-phthaloylamino-1-naphthol (4·7 g.) dissolved in pyridine (20 ml.). The mixture was kept overnight and then poured into water (150 ml.) containing potassium hydroxide (10 g.), and the solution freed from inorganic sulphate with aqueous barium chloride and concentrated. Acidification (acetic acid) of the concentrate gave an unidentified substance (3·2 g.), m. p. 150—153°. The solution was filtered, boiled for 10 min., cooled, extracted with ether to remove acetic acid, the presence of which was found to prevent precipitation of the ester, and acidified with concentrated hydrochloric acid. One crystallisation of the product as before gave the ester (0·5 g., 12%), m. p. 224—225°, undepressed with material from (*a*).

In another experiment with 2-phthaloylamino-1-naphthol (1·65 g.), the substance of m. p. 150—153° was precipitated as before, the filtrate made alkaline, evaporated under reduced pressure, and extracted with 95% ethanol, and the filtered extract was heated under reflux with hydrazine hydrate (0·5 g.) for 4 hr. Concentration of the ethanolic solution to 10 ml. and dilution with an equal volume of water, followed by acidification with concentrated hydrochloric acid failed to yield the required ester. The solution was brought to pH 4 with aqueous sodium hydroxide and acetic acid, and the ester (75 mg., 5%), m. p. 222—225° (decomp.), isolated as above.

Oxidation of 2-Naphthylamine with Persulphate.—2-Naphthylamine (5 g.), in a mixture of pyridine (200 ml.), water (600 ml.), and 2N-sodium hydroxide (30 ml.), was treated with sodium persulphate (8·3 g.) in aqueous solution as before. After 24 hr. the solution was filtered, evaporated to 100 ml. under reduced pressure, and washed with ether (3 × 150 ml.). The ice-cold solution was acidified with concentrated hydrochloric acid and, after some hours, crude 2-amino-1-naphthyl hydrogen sulphate (2·8 g., 45%) collected, as a pink powder. The ester was purified by dissolving it in a minimum amount of aqueous N-sodium hydroxide, boiling the solution with charcoal for 30 min., and re-precipitating the acid in the presence of an equal volume of acetone and a trace of sodium dithionite. After three such treatments, the acid formed pale pink prisms, m. p. 225° (decomp.), undepressed in admixture with a specimen prepared by the reduction of 2-nitro-1-naphthyl hydrogen sulphate (Found: S, 13·8; N, 6·1. Calc. for $C_{10}H_9O_4NS$: S, 13·4; N, 5·9%).

The *sodium* (Found: N, 5·2. $C_{10}H_8O_4NSNa$ requires N, 5·4%) and *potassium* (Found: N, 5·0. $C_{10}H_8O_4NSK$ requires N, 5·05%) salts (prepared from the acid) separated from 90% ethanol as pale pink and silvery-grey plates respectively. Solutions of the salts had faint blue fluorescence in daylight and strong blue fluorescence in ultra-violet light.

Hydrolysis of the acid (0·5 g.) with 5N-sulphuric acid at 100° for 30 min. gave 2-amino-1-naphthol sulphate (0·46 g.), separating from the cooled solution as grey plates. The dibenzoyl derivative crystallised from ethanol as needles, m. p. and mixed m. p. 180° (Found: N, 3·9. Calc. for $C_{24}H_{17}O_3N$: N, 3·8%). The diacetyl derivative separated from aqueous ethanol as needles, m. p. and mixed m. p. 117—118°.

Investigation of the Neutral Fraction from the Oxidation of 2-Naphthylamine with Persulphate.—2-Naphthylamine (5 g.), dissolved in water (4 l.) and 2N-sodium hydroxide (20 ml.), was treated with sodium persulphate (8·5 g.) at 80°. After 8 hr. the precipitate (1·8 g.) was separated, and 2-amino-1-naphthyl hydrogen sulphate (3·4 g., 39·5 %) was recovered from the filtrate by extraction (20 times) with butanol. The neutral precipitate was extracted with boiling benzene (4 × 100 ml.) [to leave a dark amorphous residue (1·1 g.)], and the benzene-soluble fraction was chromatographed on alumina. Elution of the column with benzene yielded: (*a*) 1 : 2-5 : 6-dibenzophenazine (88 mg.) separating from glacial acetic acid as pale yellow needles, m. p. and mixed m. p. 282—283° (Found: N, 10·0. Calc. for $C_{20}H_{12}N_2$: N, 9·9%), and (*b*) a substance (5 mg.) separating from benzene as red needles, m. p. 279°. Elution of the column with benzene–ether gave 2-2′-naphthylamino-1 : 4-naphthaquinone 4-2′-naphthylimide (I; R = 2-$C_{10}H_7$) (230 mg.), which crystallised from benzene as red needles, m. p. 252—253° (Found: C, 84·7, 85·1; H, 4·9, 5·6; N, 6·65. Calc. for $C_{30}H_{20}ON_2$: C, 84·9; H, 4·75; N, 6·6%), undepressed in admixture with synthetic material (see below) of m. p. 246—247°.

2-2′-Naphthylamino-1 : 4-naphthaquinone 4-2′-Naphthylimide (I; R = 2-$C_{10}H_7$).—2-Nitroso-1-naphthol (1 g.) and 2-naphthylamine (1·8 g.) in glacial acetic acid (20 ml.) were heated under reflux for 30 min. The product crystallised from ethyl acetate as red needles (2·1 g., 85%), m. p. 246—247° (Found: C, 84·6; H, 4·9; N, 6·7%). Meldola (*loc. cit.*) gives m. p. 246—247° for an apparently identical product.

Potassium 2-Hydroxyphenylsulphamate.—Chlorosulphonic acid (25·6 g.) was added slowly with cooling and stirring to pyridine (150 ml.), followed by *o*-aminophenol (21·6 g.). After being kept at room temperature overnight, the mixture was poured into water (500 ml.), containing potassium hydroxide (45 g.). The solution was distilled down to 150 ml., crystallisation of the product commencing. *Potassium 2-hydroxyphenylsulphamate* was obtained and was purified by the addition of ether to a solution of the salt in aqueous ethanol; it separated as plates (12 g., 27%) (Found: N, 6·3. $C_6H_6O_4NSK$ requires N, 6·2%). Its aqueous solution gave a red colour with diazotised sulphanilic acid in alkali, and no colour with *p*-dimethylaminobenzaldehyde. *o*-Aminophenyl potassium sulphate does not couple with diazotised sulphanilic acid and gives a yellow colour with *p*-dimethylaminobenzaldehyde. Heating the salt with dilute hydrochloric acid produced inorganic sulphate and, after neutralisation, *o*-aminophenol was isolated, m. p. and mixed m. p. 172—174° (Found: N, 12·7. Calc. for C_6H_7ON: N, 12·8%).

Some analyses were by Mr. F. H. Oliver of the microanalytical laboratory, Organic Chemistry Department, Imperial College of Science and Technology. The work has been supported by grants to the Royal Cancer Hospital and The Chester Beatty Research Institute from the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, the Anna Fuller Fund, and the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

THE CHESTER BEATTY RESEARCH INSTITUTE, THE INSTITUTE OF CANCER RESEARCH,
THE ROYAL CANCER HOSPITAL, LONDON, S.W.3. [*Received, July 8th*, 1953.]

---

730. *A New Synthesis of* 1 : 3-*Diketones and the Preparation of* 1-*Keto-olefins by Means of Trifluoroacetic Anhydride as Condensing Agent.*

By A. L. HENNE and J. M. TEDDER.

Solutions of carboxylic acids in trifluoroacetic anhydride, when treated with an olefin or an acetylene, yield β-trifluoroacetoxy-ketones (I) or the enol trifluoroacetate of a β-diketone (III), respectively. These compounds are then readily converted into acyl-olefins (II) or β-diketones (IV).

IT has been suggested that esterification of, and synthesis of aromatic ketones from, carboxylic acids in trifluoroacetic anhydride solution are effected by acylium ions ($R{\cdot}CO^+$), small amounts of which occur therein (Bourne, Randles, Tatlow, and Tedder, *Nature*, 1951, **168**, 949). In conformity, it has now been found possible to add the unsymmetrical anhydride ($R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3$) across double and triple bonds, simply by introducing olefins and acetylenes into these solutions.

$$R{\cdot}CO^+ + CF_3{\cdot}CO_2^- + R'{\cdot}CH{:}CHR'' \longrightarrow \underset{(I)}{R{\cdot}CO{\cdot}CHR'{\cdot}CHR''{\cdot}O{\cdot}CO{\cdot}CF_3} \longrightarrow \underset{(II)}{R{\cdot}CO{\cdot}CR'{:}CHR''} + CF_3{\cdot}CO_2H$$

$$R{\cdot}CO^+ + CF_3{\cdot}CO_2^- + R'C{:}\dot{C}H \longrightarrow \underset{(III)}{CF_3{\cdot}CO{\cdot}O{\cdot}CR'{:}CH{\cdot}CO{\cdot}R} \xrightarrow{MeOH} \underset{(IV)}{R'{\cdot}CO{\cdot}CH_2{\cdot}COR} + CF_3{\cdot}CO_2Me$$

The first products of the addition to olefins, the β-trifluoroacetoxy-ketones (I), have not been obtained pure; they decompose slowly but spontaneously to the acyl-olefins (II). As a method for the preparation of acyl-olefins it is considerably more convenient than Darzens's (*Compt. rend.*, 1910, **150**, 707) in which the olefin is treated with an acyl chloride and a Lewis acid, the intermediate product being treated with a tertiary amine, and our yields are as good (cf. Royals and Hendry, *J. Org. Chem.*, 1950, **15**, 1151). For a general reaction the carboxylic acid is dissolved in trifluoroacetic anhydride, the olefin added, and the reactants left at room temperature for 2—12 hr. The mixture is poured into aqueous sodium carbonate which rapidly releases the free acyl-olefin, and the trifluoroacetic acid can be recovered from the mother-liquor.

The addition to an acetylene has been carried out under much the same conditions. The first product, the enol trifluoroacetate (III) of a β-diketone, is much more stable than the ketol trifluoroacetate (I) and can be obtained pure. In practice it is better simply to pour the mixture into an excess of methyl alcohol and reflux this solution. Transesterific-

ation is very rapid, and the pure β-diketone is obtained by fractionation. The yields reported below are only of the order of 20%, but there is reason to believe that these might be improved.

Neither reaction has been developed exhaustively, but the preparations reported below seem to indicate a scope similar to that of the esterification and aromatic ketone syntheses (Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2976; 1951, 718). The preparation of acyl-olefins by use of trifluoroacetic anhydride, like the reactions reported previously, provides an extremely simple and mild method of performing a well-established reaction. The synthesis of β-diketones directly from carboxylic acids and acetylenes provides a new route to these important compounds.

Experimental

cyclo*Hexenyl Methyl Ketone*.—(*a*) *cyclo*Hexene (18·5 c.c.) was added to a solution of acetic acid (10·5 c.c.) in trifluoroacetic anhydride (27·0 c.c.). A yellow colour developed rapidly and the temperature rose to, and remained at, 37° for about 1 hr., during which the colour deepened. After a total of 2·5 hr. the mixture was poured on crushed ice and sodium hydrogen carbonate. The product was extracted with ether and dried ($MgSO_4$). Evaporation left a brown sweet-smelling liquid which contained fluorine. The principal fraction (13·5 g.) boiled at 94—98°/33 mm., and had n_D^{26} 1·4605, d_4^{27} 1·021. This proved to be a 3 : 2 mixture of *cyclo*hexenyl methyl ketone and 2-acetyl*cyclo*hexyl trifluoroacetate. Treatment with 0·1N-sodium hydroxide converted it all into the olefinic ketone (48·1%), b. p. 86—88°/28 mm., n_D^{28} 1·4885. The semicarbazone had m. p. 217—219°. Kon (*J.*, 1926, 1801) reported b. p. 81°/13 mm., n_D^{20} 1·49042, and for the semicarbazone m. p. 217°.

(*b*) *cyclo*Hexene (10·1 c.c.) was treated with trifluoroacetic anhydride (14·2 c.c.) and acetic acid (5·7 c.c.). After 2·5 hr. the mixture was poured into water (instead of sodium hydrogen carbonate solution), and the products were extracted with ether, washed repeatedly with water and finally dilute sodium hydrogen carbonate solution, and dried ($MgSO_4$). After evaporation, the principal fraction (b. p. 58—62°/6 mm., n_D^{25} 1·4450), was a sweet-smelling, and initially a colourless and neutral liquid. It gradually darkened and soon became strongly acid. This fraction (6·3 g.) was refluxed with methyl alcohol (10 c.c.) for 1·5 hr. The low-boiling material (b. p. 52—63°) was then distilled off, collected, and treated with gaseous ammonia. Evaporation of the excess of methyl alcohol left crude trifluoroacetamide, m. p. 69—70°. The residual high-boiling material was distilled, and the first few drops of distillate were cloudy and consisted partly of water. The main fraction (b. p. 56°/2·5 mm., n_D^{24} 1·4878; 3·83 g.) was *cyclo*hexenyl methyl ketone.

cyclo*Hexenyl Propyl Ketone*.—Butyric acid (9·2 c.c.) was added to trifluoroacetic anhydride (14·0 c.c.) and *cyclo*hexene (10·1 c.c.). The mixture became very warm and darkened rapidly, and it was cooled in water (12°) until the reaction had subsided. It was then left for 2·5 hr. and poured on crushed ice and sodium hydrogen carbonate. When all the acid present had been neutralised the ketol trifluoroacetate was separated and poured into concentrated sodium carbonate solution with which it was shaken for 20 min. The organic layer, which now consisted almost entirely of *cyclo*hexenyl propyl ketone was extracted with ether and dried ($MgSO_4$). Evaporation of the ether and a trace of unchanged *cyclo*hexene left a sweet-smelling liquid, which was distilled. These fractions were taken : (i) b. p. 67—77°/5 mm., n_D^{21} 1·4505, 2·41 g.; (ii) b. p. 77—81°/5 mm., n_D^{21} 1·4680, d_4^{20} 0·95, 6·06 g.; (iii) b. p. 81—97°/5 mm., 1·05 g. Fraction (i) consisted of *cyclo*hexenyl propyl ketone contaminated with a fluorine-containing compound, probably *cyclo*hexyl trifluoroacetate [this ester, b. p. 151·5°, n_D^{25} 1·3801, is formed by the direct addition of trifluoroacetic acid to *cyclo*hexene (Zimmer and Henne, unpublished work)]. The whole fraction was treated with gaseous ammonia and then washed with water (ammonia would convert *cyclo*hexyl trifluoroacetate into trifluoroacetamide and *cyclo*hexanol, both water-soluble), and the upper layer was separated and dried (n_D^{23} 1·4685, 1·7 g.). Fraction (ii) consisted of almost pure *cyclo*hexenyl propyl ketone, and fraction (iii) was not investigated in detail, but contained traces of fluorine and probably consisted of 2-butyryl*cyclo*hexyl trifluoroacetate contaminated with polymeric material. The yield of *cyclo*hexenyl propyl ketone was 7·8 g. (51%). Its semicarbazone had m. p. 172·5°. Darzens and Rost (*Compt. rend.*, 1910, **151**, 758) reported *cyclo*hexenyl propyl ketone, b. p. 113—114°/7 mm., and for the semicarbazone, m. p. 171°.

Oct-3-en-2-one.—Hex-1-ene (12·5 c.c.) was added to a solution of acetic acid (5·6 c.c.) in trifluoroacetic anhydride (14·0 c.c.), kept at room temperature (26°) for 20 min., warmed at 40°

for 1·5 hr., and finally left at room temperature (26—27°) for 14 hr. At the end of this time the mixture was poured into aqueous sodium carbonate solution and was then stirred with excess of sodium carbonate for 1 hr. The alkaline mixture was extracted with ether and dried ($MgSO_4$), and the ether evaporated off. The residue was distilled and the temperature rose steadily; four fractions were taken. Fraction (i), b. p. 35—45°/5 mm., n_D^{25} 1·4366, contained no fluorine and gave a semicarbazone, m. p. 110—111°. Fraction (ii), b. p. 45—50°/5 mm., n_D^{25} 1·4332, contained a trace of fluorine and gave a semicarbazone, m. p. 110—112°. Fraction (iii), b. p. 50—55°/5 mm., n_D^{25} 1·3965, contained fluorine, and gave a semicarbazone, m. p. 109—111°. Fraction (iv), b. p. 60—95°/5 mm., n_D^{25} 1·4270, contained a trace of fluorine and gave no semicarbazone. Fractions (i) and (ii) consisted of oct-3-en-2-one, fraction (ii) containing just a trace of the ketol trifluoroacetate. Fraction (iii) also consisted principally of oct-3-en-2-one with an appreciable proportion of the ketol trifluoroacetate. The proportion of trifluoroacetate, estimated by treating a weighed portion of fraction (iii) with standard alkali, was found to be 41%. Fraction (iv) consisted of polymeric material which was not investigated and there was a residue of polymer (0·96 g.) which was not distilled. Total yields were : oct-3-en-2-one 2·69 g. (22%) and 1-acetylhexyl trifluoroacetate 0·33 g. (1·4%). *Oct-3-en-2-one semicarbazone* had m. p. 111—112° (Found: C, 59·3; H, 9·3. $C_9H_{17}ON_3$ requires C, 59·0; H, 9·3%).

Octane-2 : 4-dione.—(*a*) Hex-1-yne (11·4 c.c.) was added to acetic acid (5·7 c.c.) and trifluoroacetic anhydride (14·5 c.c.). A red-brown colour developed immediately, which darkened slowly while the mixture was left at room temperature (27°) for 18 hr. Methyl alcohol (25 c.c.) was then added and the mixture was refluxed for 90 min. The first product collected on distillation was methyl trifluoroacetate, b. p. 41°, n_D^{25} 1·3057; this was followed by mixtures of methyl acetate and unchanged methanol boiling between 60° and 65°. No further material came over at atmospheric pressure and the remaining products were distilled under reduced pressure. Fraction I, b. p. 45—50°/3·5—4·0 mm. (mainly at 48°/3·5 mm.), n_D^{25} 1·4484 (2·41 g.), was pure octane-2 : 4-dione. Fraction II, b. p. 50—75°, n_D^{25} 1·4471 (0·57 g.), was dione contaminated with polymeric material. There was a residue of non-volatile material (3·9 g.). The total yield of octane-2 : 4-dione was 2·84 g. (20·2%). A portion of fraction II treated with cupric acetate gave a 75% yield of the dione copper chelate complex, m. p. 143·5—144·5° (Found: C, 55·0; H, 7·9. Calc. for $C_{16}H_{28}O_4Cu$: C, 55·2; H, 8·1%). Morgan and Holmes (*J.*, 1924, **125**, 761) reported the copper derivative, m. p. 143°. Semicarbazide gave a product, m. p. 89°; Hurd and Kelso (*J. Amer. Chem. Soc.*, 1940, **62**, 2186) reported 5-butyl-3-methylpyrazole-1-carboxyamide, m. p. 89—90°.

(*b*) Acetic acid (5·7 c.c.) was added to hex-1-yne (11·4 c.c.) and trifluoroacetic anhydride (14·0 c.c.) and left for 2·5 hr., before it was poured into ice-water. The products were separated by extraction with ether, and the extract was washed thoroughly with sodium hydrogen carbonate solution and distilled water. The ethereal solution was dried ($MgSO_4$) and evaporated and the main product distilled. A single high-boiling fraction (b. p. 58—60/4—5 mm., n_D^{25} 1·4287, containing fluorine) was obtained. This was treated with methanol and after 90 min.' refluxing the low-boiling products were distilled off and collected. This distillate which consisted of methyl trifluoroacetate and unchanged methanol was treated with gaseous ammonia, and the excess of methanol evaporated, to leave trifluoroacetamide, m. p. 71°. The residue was treated with cupric acetate solution and yielded octane-2 : 4-dione copper chelate complex, m. p. 143·4°.

3-Oxo-octanoylbenzene.—Trifluoroacetic anhydride (18·4 c.c.) was added to a mixture of hex-1-yne (14·9 c.c.) and benzoic acid (16·0 g.). The acid dissolved slowly and the solution developed a pink colour which deepened rapidly. After 17 hr. at room temperature, methyl alcohol (30 c.c.) was added and the solution heated under reflux for 2 hr. Methyl trifluoroacetate and unchanged methyl alcohol were distilled off at atmospheric pressure, the remaining volatile components being collected *in vacuo*, leaving a dark residue (6·3 g.). Distillation was hampered by unchanged benzoic acid which crystallised throughout the distillation apparatus so that no discrete fractions could be taken. The whole distillate was treated with sodium hydrogen carbonate solution, followed by cupric acetate. The copper derivative of the diketone was isolated by chloroform-extraction, the yield after a single recrystallisation being 4·01 g. (17%). Two further recrystallisations were necessary to obtained a constant m. p. of 124—125°. This diketone was described by Beyer and Claisen (*Ber.*, 1887, **20**, 2178) as a liquid, b. p. 183—184°/30 mm., forming a copper derivative (no m. p. given).

Department of Chemistry, The Ohio State University,
Columbus 10, Ohio, U.S.A.

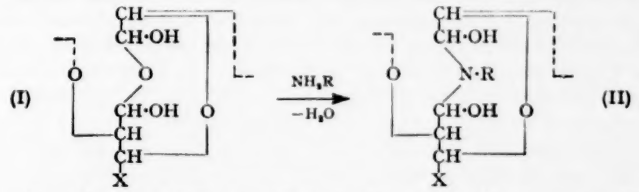
[*Received, June 22nd*, 1953.]

731. *Properties of Periodate-oxidised Polysaccharides. Part II.* The Structure of Some Nitrogen-containing Polymers.*

By Vincent C. Barry and P. W. D. Mitchell.

Cyclic structures are proposed for periodate-oxidised polysaccharides and for the polymers obtained on reaction with hydrazides and other bases.

In Part I* nitrogen-containing polymers prepared from periodate-oxidised starch (oxystarch) were described. Analysis of these, and of others of a similar kind from alginic acid and inulin, has shown that they contain only one molecule of reagent per hexose unit, instead of two, as would be expected from reaction with a hexose unit containing two free aldehyde groups. The aldehyde functions of the oxy-hexose units are apparently modified in some way and it is suggested that they are united by a " hemialdal " linkage to give a seven-membered cyclic unit (I; X = CH_2·OH), which reacts with the base as follows:



The mechanism of the periodate oxidation of α-glycols has been studied by various workers (Criegee, *Sitzungsber. Ges. Beford. Naturwiss. Marburg*, **1934**, **69**, 25; Criegee, Kraft, and Rank, *Annalen*, **1933**, **507**, 159; Price and Knoll, *J. Amer. Chem. Soc.*, **1938**, **60**, 2726; Price and Knell, *ibid.*, **1942**, **64**, 552; Duke, *ibid.*, **1947**, **69**, 3054) and it has been suggested by Criegee that an intermediate in the reaction is a cyclic ester formed between the reagent and the α-glycol group. If this is correct it is reasonable to suppose that, throughout the reaction, the parent structure is retained and that a condensation (as hydrates) of the liberated aldehyde groups occurs through the pair of carbon atoms which formed the original α-glycol group.

A hemialdal linkage of this kind is embodied in one of the cyclic structures proposed by Hurd and his co-workers (Hurd, Baker, Holysz, and Saunders, *J. Org. Chem.*, **1953**, **18**, 186) to explain the absence, as deduced from spectrophotometric data, of carbonyl groups in periodate-oxidised methyl α-D-glucopyranoside. Such a structure contains an extra molecule of water not present in the dialdehyde, and it is significant, in this connection, that the crystalline dialdehydes obtained from four different 6-deoxy-methylaldohexopyranosides (Dayton, MaClay, Hann, and Hudson, *J. Amer. Chem. Soc.*, **1939**, **61**, 1660) gave analyses agreeing with requirements for monohydrates. Furthermore, when heated in a vacuum to 65° over anhydrone, they sublimed without change in composition.

Spectrophotometric examination of oxycellulose (Rowen, Forziati, and Reeves, *ibid.*, **1951**, **73**, 4484) yielded no evidence of the existence of carbonyl groups. This result does not lend support to the structure proposed for oxystarch by Michell and Purves (*ibid.*, **1942**, **64**, 589), in which the aldehyde group at $C_{(3)}$ is visualised as forming a hemialdal linkage with the secondary alcoholic group at $C_{(6)}$, thus yielding a D-erythrofuranose ring, whilst the aldehyde group at $C_{(2)}$ remains free. Rowen *et al.* (*loc. cit.*) showed that light absorption due to carbonyl groups was still absent in the dialdehyde prepared from methyl 4 : 6-*O*-benzylidene-α-D-glycoside. Here there is no possibility of acetal formation, and these authors were of the opinion that the aldehyde groups were modified by hydration.

In the cyclic structure (I) $C_{(2)}$ and $C_{(3)}$ are asymmetric. Reactions taking place with the aldehyde groups in this cyclised form might be expected to be accompanied by rotational changes such as are observed when a solution of oxystarch is treated with various reagents. When ammonia or sodium *p*-aminobenzoate was added to a solution of oxystarch, marked

* Part I, *J.*, 1953, 3610.

changes in the rotation of the solution occurred. With both reagents, an initial rapid fall from a *dextro-* to a *lævo*-value was followed by a slower return to a dextrorotatory value. From the oxystarch solution to which sodium *p*-aminobenzoate had been added and in which such rotational changes had taken place, a polymeric nitrogen-containing substance was isolated. These changes in rotation were in contrast to those obtained when oxystarch was treated with sodium hydroxide (cf. Head, *J. Text. Inst.*, 1947, **38**, 1395). An initial rise followed by a slow fall in rotation was accompanied by the disappearance of the potential aldehyde functions, possibly through the medium of an internal Cannizzaro reaction (Fry, Wilson, and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 873), and after an hour no polymer was obtained on addition of isoniazid to the neutralised solution.

Evidence in support of structure (II) for the nitrogen-containing polymers has been obtained by degradation. When the oxystarch–isoniazid polymer was boiled with 50% acetic acid, crystalline glyoxal bis*iso*nicotinoylhydrazone separated. [The monohydrazone of glyoxal which is, presumably, formed first has been shown to be converted, under the above conditions, into the bishydrazone (Barry and Mitchell, *J.*, 1953, 3610)]. Degradation with phenylhydrazine and *cyclo*hexylamine proceeded in different ways. The former reagent yielded glyoxal bisphenylhydrazone and the latter, glyoxal bis*iso*nicotinoyl hydrazone. These different products could arise from the proposed cyclic structure (II) by scission at the $C_{(2)}$–N and $C_{(3)}$–N bonds, respectively. A somewhat similar result was obtained with the isoniazid polymer of alginic acid which may be formulated as (II; X = CO_2H). Degradation with acetic acid gave, in this case, glyoxal bis*iso*nicotinoylhydrazone, whereas phenylhydrazine and *cyclo*hexylamine yielded glyoxal bisphenylhydrazone, and the double Schiff base of glyoxal and *cyclo*hexylamine, respectively. No derivatives of the other fragment of the molecule separated during these degradations, but this is not surprising in view of the experiences of other workers. The D-erythrose part of oxidised starch or cellulose has only been characterised by conversion of the dialdehydes into diacids or dialcohols before hydrolysis (Jayme and Maris, *Ber.*, 1944, **77**, 383; Abdel-Akher, Hamilton, Montgomery, and Smith, *J. Amer. Chem. Soc.*, 1952, **74**, 4970).

The polymer obtained from the reaction of oxyinulin with isoniazid proved to be quite resistant to the methods used to degrade those derived from starch and alginic acid. The composition of this polymer was again approximately that required for the addition of one isoniazid molecule to each hexose unit. In contrast to the 7-membered ring which arises from the pyranose structure of starch, the furanose structure of inulin may form a six-membered cyclic structure both in the dialdehyde and in the isoniazid polymer. This may be a reason for the increased stability of the polymer although construction of molecular models showed that both rings are apparently strainless. In the larger seven-membered ring, however, an element of conformational instability is introduced because the substituents on two adjacent carbon atoms must be in the true *cis*-position (for a review, see Reeves, *Adv. Carbohydrate Chem.*, 1952, **6**, 108).

Experimental

Oxyinulin–Isoniazid Polymer.—Inulin {2 g.; $[\alpha]_D^{21}$ −35·3° (*c*, 0·957 in H_2O)} was added to an aqueous solution (1·25%; 250 c.c.) of sodium metaperiodate. The polysaccharide dissolved to give a clear solution which, after 48 hr., was reduced, while cooled in ice-water, with sulphur dioxide. The solution was neutralised with aqueous sodium hydrogen carbonate and made slightly acid by the addition of dilute acetic acid. Addition of isoniazid (2 g.) in water (20 c.c.) gave a white precipitate which was separated in the centrifuge and washed with water, methanol, and ether. The white amorphous *polymer* (2·12 g.) was dried in the vacuum-oven at 100° (P_2O_5) for 2 hr. (Found: C, 43·6; H, 5·6; N, 12·1. $C_{12}H_{13}O_5N_3,H_2O$ requires C, 48·5; H, 5·1; N, 14·1%).

Oxyalginic Acid–Isoniazid and –Thiosemicarbazide Polymers.—Sodium alginate ("Manucol"; 2 g.) was treated with a solution of sodium metaperiodate (1·25%; 214 c.c.). A clear solution was obtained and after 48 hr. 0·008 mole of periodate had been consumed. Ethylene glycol (5 c.c.) was added to the solution which was then dialysed against running water for 11 days. The dialysed solution was found, by evaporation of an aliquot portion, to contain 6·45 g./l. of oxidised material and had $[\alpha]_D^{22}$ +133°. Two 50-c.c. portions of this solution were treated

with aqueous solution of isoniazid (50 c.c.; 1·15%) and thiosemicarbazide (50 c.c.; 1·12%). After 16 hr., acidification with dilute acetic acid gave amorphous precipitates which were isolated as above. The pale yellow isoniazid polymer weighed 0·394 g. (Found: C, 43·1, 45·5, 43·2; H, 5·2, 4·0, 5·0; N, 11·9, 13·8, 13·1. $C_{13}H_{11}O_6N_3,H_2O$ requires C, 46·5; H, 4·1; N, 13·6%). The *thiosemicarbazide* polymer (0·196 g.) was white (Found: C, 30·9, 29·7; H, 4·4, 4·5; N, 17·5, 17·5; S, 13·5, 13·0. $C_7H_9O_5N_3S,H_2O$ requires C, 31·7; H, 4·2; N, 15·9; S, 12·1%).

Degradation of Oxyalginic Acid–Isoniazid Polymer.—(a) *With acetic acid.* The polymer (0·5 g.) was refluxed with 50% acetic acid (15 c.c.) for 10 min. A clear brown solution was obtained which, on cooling, gave well-defined colourless rectangular crystals of glyoxal bis*iso*nicotinoylhydrazone, m. p. >360°, $\lambda_{max.}$ 366 mμ in 0·1N-sodium hydroxide (Barry and Mitchell, *loc. cit.*).

(b) *With phenylhydrazine.* The polymer, dissolved in sodium hydrogen carbonate solution, was treated with aqueous phenylhydrazine acetate. The yellow precipitate obtained was dissolved by warming the solution to which had been added a small quantity of ethanol. On cooling, characteristic saw-shaped yellow crystals of glyoxal bisphenylhydrazone separated, having m. p. 167—169° and mixed m. p. 168°.

(c) *With* cyclo*hexylamine.* A solution of the polymer (100 mg.) in saturated sodium hydrogen carbonate solution (5 c.c.) was treated with *cyclo*hexylamine (1 c.c.) in ethanol (3 c.c.). After 2 hr., solid material which had separated was redissolved by warming, and, on cooling, colourless spear-shaped crystals of the double Schiff base of glyoxal and *cyclo*hexylamine were obtained (m. p. 147—179°; mixed m. p. 148—149°).

Degradation of Oxystarch–Isoniazid Polymer.—(a) *With acetic acid.* The polymer described in Part I (0·5 g.) was refluxed with 50% acetic acid for 2 hr. The dark brown solution, on cooling, gave colourless rectangular plates (136 mg.) of glyoxal bis*iso*nicotinoylhydrazone, m. p. >360°, $\lambda_{max.}$ 366 mμ in 0·1N-sodium hydroxide.

(b) *With phenylhydrazine.* The polymer was dissolved in warm 50% acetic acid, and phenylhydrazine added to the cooled solution. After 24 hr., a reddish-brown product was obtained which on recrystallisation from aqueous methanol had m. p. 169°, unchanged on admixture with authentic glyoxal bisphenylhydrazone.

(c) *With* cyclo*hexylamine.* Treatment of a solution of the polymer in 50% acetic acid with a few drops of *cyclo*hexylamine gave, after 24 hr., colourless needles of glyoxal bis*iso*nicotinoylhydrazine, m. p. >360°, $\lambda_{max.}$ 366 mμ in 0·1N-sodium hydroxide. The degradation was not caused by the method of solution of the polymer since in a parallel experiment in which addition of *cyclo*hexylamine was omitted no solid separated.

Rotational Measurements.—The following Tables give the changes in the rotation of oxidised polysaccharide solutions on addition of dilute aqueous ammonia, sodium *p*-aminobenzoate, and sodium hydroxide. Measurements were made at 22° in 2-dm. tubes at intervals, until the solutions became too dark. 0·0585M-Sodium metaperiodate was used throughout.

(i) *With ammonia.* (*a*) Amylose (1·139 g.) was treated with periodate solution (144 c.c.) and after 44 hr., 0·0063 mole of oxidant had been consumed. The oxyamylose was separated by filtration and washed with water until free from iodate and periodate. The product was dissolved in water (100 c.c.) on the water-bath in 1 hr. The concentration of the solution of oxyamylose thus obtained was determined by evaporation to dryness of an aliquot portion. To 10 c.c. of this solution (1·088%), 10% aqueous ammonia (0·5 c.c.) was added and the change in rotation of the solution followed:

t (min.) ...	0	2	5	10	15	20	30	35
α	+0·52°	−0·71°	−0·61°	−0·46°	−0·35°	−0·26°	−0·15°	−0·05°
t (min.) ...	45	50	60	80	145	210	260	330
α	+0·13°	+0·17°	+0·24°	+0·34°	+0·55°	+0·69°	+0·72°	+0·80°

(*b*) Amylopectin (2 g.) was treated with periodate solution (252 c.c.) and after 44 hr. 0·0114 mole of oxidant had been consumed. From the product, treated as above, a solution (1·666%) of oxyamylopectin was obtained and the rotational changes on addition of ammonia (0·5 c.c.; 10%) to 10 c.c. of the solution were measured:

t (min.) ...	0	1	2	5	10	15	20	26
α	+0·70°	−1·07°	−0·97°	−0·77°	−0·53°	−0·36°	−0·29°	−0·09°
t (min.) ...	31	40	65	76	90	100	120	130
α	−0·05°	+0·19°	+9·45°	+0·56°	+0·58°	+0·66°	+0·68°	+0·69°

(*c*) Waxy maize starch (2 g.), treated with sodium metaperiodate solution (252 c.c.), consumed 0·0115 mole of oxidant in 44 hr. A 1·999% solution of the oxidised polysaccharide was obtained and treated with ammonia as above :

t (min.) ...	0	2	5	10	15	20	25	30	35	40
α	+0·81°	−0·26°	−1·14°	−0·87°	−0·67°	−0·47°	−0·36°	−0·22°	−0·11°	−0·04°
t (min.) ...	45	50	60	70	100	150	220	310	360	
α	+0·06°	+0·14°	+0·24°	+0·34°	+0·52°	+0·82°	+0·96°	+1·05°	+1·07°	

(*d*) Floridean starch was isolated from *Dilsea edulis* by the method described by Barry, Halsall, Hirst, and Jones (*J.*, 1949, 1468). The starch (2 g.) was oxidised with periodate solution (252 c.c.) and consumed in 44 hr. 0·0115 mole of oxidant. The polysaccharide dissolved and, after addition of ethylene glycol (5 c.c.) to the solution, it was dialysed against running water for 12 days. The addition of ammonia was made as before (*c* 0·84) :

t (min.)	0	2	3	5	10	20	30
α	+0·24°	−0·59°	−0·61°	−0·57°	−0·39°	−0·37°	−0·23°
t (min.)	38	105	124	233	297	308	540
α	−0·21°	+0·04°	+0·05°	+0·17°	+0·20°	+0·21°	+0·29°

(*e*) Sodium alginate (2 g.) was treated with periodate (214 c.c.) and consumed in 46 hr. 0·008 mole of oxidant. The alginate dissolved to give a clear solution, which was dialysed for 11 days after addition of ethylene glycol (5 c.c.). A 0·645% solution of oxyalginate was obtained, 10 c.c. of which were treated with ammonia as above :

t (min.) ...	0	1	5	10	19	25	29	38
α	+1·75°	+1·49°	+1·38°	+1·29°	+1·12°	+1·03°	+1·01°	+0·90°
t (min.) ...	45	51	60	71	99	112	156	
α	+0·84°	+0·80°	+0·70°	+0·65°	+0·46°	+0·41°	+0·18°	

(ii) *With sodium* p-*aminobenzoate*. Potato starch (5 g.), treated with periodate solution (580 c.c.), consumed 0·026 mole of oxidant. The product, washed with water until free from periodate and iodate, was dissolved in warm water to give a 2% solution. To 10-c.c. quantities of this solution was added sodium *p*-aminobenzoate which dissolved readily giving clear solutions whose rotations in a 1-dm. tube were followed :

(*A*) Sodium *p*-aminobenzoate added : 0·249 g.

t (min.) ...	0	3	5	10	18	24	34	44	57	67
α	+0·91°	+0·51°	+0·44°	+0·34°	+0·28°	+0·27°	+0·26°	+0·26°	+0·31°	+0·37°
t (min.) ...	74	83	103	117	137	147	177	192	388	
α	+0·39°	+0·42°	+0·48°	+0·49°	+0·55°	+0·58°	+0·60°	+0·63°	+0·74°	

(*B*) Sodium *p*-aminobenzoate added : 0·500 g.

t (min.) ...	0	1·5	2	3	5	11	14	24	37
α	+0·91°	+0·16°	+0·07°	−0·03°	−0·10°	−0·11°	−0·09°	−0·07°	−0·02°
t (min.) ...	59	72	81	91	101	111	119	145	325
α	+0·07°	+0·12°	+0·12°	+0·17°	+0·18°	+0·20°	+0·25°	+0·30°	+0·42°

(*C*) Sodium *p*-aminobenzoate added : 0·750 g.

t (min.) ...	0	1·5	2·5	4·5	6	10	15	20	25	28
α	+0·91°	−0·26°	−0·40°	−0·45°	−0·44°	−0·38°	−0·34°	−0·31°	−0·29°	−0·29°
t (min.) ...	35	54	60	65	70	131	143	150	217	390
α	−0·29°	−0·24°	−0·21°	−0·20°	−0·16°	+0·05°	+0·09°	+0·09°	+0·24°	+0·24°

After 48 hr., the dark solution was acidified with dilute acetic acid, and the yellow precipitate obtained was separated in the centrifuge. The amorphous *product* was washed with water and precipitated from solution in ethanol with ether. A yellow powder (250 mg.) was obtained (Found : C, 50·6; H, 5·6; N, 3·8. $C_{13}H_{15}O_7N$ requires C, 52·5; H, 5·1; N, 4·7%).

(*D*) Sodium *p*-aminobenzoate added : 1·250 g.

t (min.) ...	0	2·5	5	10	15	20	25	30
α	0·91°	−0·79°	−0·76°	−0·65°	−0·62°	−0·53°	−0·50°	−0·46°
t (min.) ...	35	41	51	57	128	150	300	352
α	−0·44°	−0·44°	−0·35°	−0·32°	−0·10°	−0·09°	−0·01°	+0·08°

(iii) *With sodium hydroxide.* 2N-Sodium hydroxide (1 c.c.) was added to a 2% solution of oxystarch (20 c.c.) and the rotational changes of the mixture in a 2-dm. tube were noted :

t (min.) ...	0	3·5	5	5·5	6·5	7·5	8	20·5	22	97
α	+1·10°	+1·74°	+1·89°	+1·87°	+1·84°	+1·90°	+1·90°	+1·86°	+1·92°	+1·68°

Next morning, the dark solution when acidified with dilute acetic acid, gave no precipitate with isoniazid.

One of us (P. W. D. M.) is indebted to University College, Dublin, for the award of a Lasdon Foundation Research Fellowship. We are grateful to Professor S. Peat, F.R.S., and Professor T. Dillon for various samples.

LABORATORIES OF THE MEDICAL RESEARCH COUNCIL OF IRELAND,
TRINITY COLLEGE, DUBLIN. [*Received, July 29th,* 1953.]

---

732. *The Preparation and Properties of Some Alkyl β-D-Glucopyranoside Tetranitrates.*

By D. M. SHEPHERD.

Ethyl, *n*-propyl, and *n*-butyl β-D-glucopyranoside tetranitrate have been prepared. Their solubilities in water have been determined and their mode of hydrolysis with dilute alkali has been studied.

DURING a study of the pharmacology of certain organic nitrates it has been necessary to prepare a series of alkyl β-D-glucopyranoside tetranitrates some of which have not previously been described. Since the pharmacological behaviour of these compounds is related to their mode of hydrolysis and to their solubility in water, particular attention has been paid to these properties in the present work. The results, which are summarized in the Table, include comparative studies carried out at the same time on the already known compounds methyl α-D-glucopyranoside tetranitrate (Will and Lenze, *Ber.*, 1898, **31**, 68) and the β-anomer (Bell and Synge, *J.*, 1937, 1711).

Baker and Easty (*J.*, 1952, **1193**) showed that the hydrolysis of organic nitrates may involve three distinct but simultaneous mechanisms, *viz.*, (*a*) nucleophilic substitution with formation of the parent alcohol together with nitrate ions, (*b*) β-hydrogen elimination with formation of an olefin and nitrate ions, and (*c*) α-hydrogen elimination with formation of a carbonyl compound (aldehyde or ketone) and nitrite ions. Nef (*Annalen*, 1899, **309**, 126) observed the formation of ethers during the alkaline hydrolysis of methyl, ethyl, and higher alkyl nitrates, while the formation of cyclic ethers (anhydro-sugars) has been demonstrated in the alkaline hydrolysis of certain sugar nitrates (Gladding and Purves, *J. Amer. Chem. Soc.*, 1944, **66**, 76; Ansell, Honeyman, and Williams, *Chem. and Ind.*, 1952, 149; Ansell and Honeyman, *J.*, 1952, 2778). In studies of a series of methyl α- and β-D-glucopyranoside mononitrates from which all free hydroxyl groups were excluded by methylation or acetylation, Gladding and Purves (*loc. cit.*) found that, while the acetate groups were hydrolysed almost instantaneously by alkali, the single nitrate group (except when attached to $C_{(1)}$) was removed quite slowly. In some cases the hydrolysis was not complete even after 100 hours.

Alkyl group	Conditions *	NaOH used (equivs. per mole of tetranitrate)	NO_3^- formed (equivs. per mole of tetranitrate)	Residual NO_3^- (equivs. per mole of tetranitrate)	Solubility at 20° (g./l.)
α-Me	R.T., 2 hr.	4·3	2·92	0·83	0·04493
,, ...	Reflux, 3 hr.	5·4	3·11	—	—
β-Me	R.T., 1 hr.	3·8	3·02	—	0·07586
,, ...	R.T., 2 hr.	4·2	2·96	0·87	—
,, ...	Reflux, 3 hr.	5·7	2·98	—	—
β-Et	R.T., 2 hr.	4·3	2·97	0·91	0·01328
β-Pr^n	,,	4·4	3·19	0·85	0·00387
β-Bu^n	,,	4·2	3·09	0·80	0·00211

* R.T. = room temperature.

In the present work it has been found that hydrolysis of alkyl D-glucopyranoside

tetranitrates in 0·1N-methanolic sodium hydroxide is rapid, the four equivalents of alkali theoretically required being consumed in 1—2 hours. At this stage the solution contains three equivalents of alkali nitrate per molecule. When the hydrolysis is carried out under more drastic conditions, 3 hours under reflux, the consumption of alkali increases to 5·7 equivalents while the nitrite liberated remains constant at 3 equivalents. These figures indicate that the additional alkali is used for further degradation of the primary products of hydrolysis rather than for further denitration. Similar observations have been reported for the alkaline hydrolysis of glycerol trinitrate (Berl and Delpy, *Ber.*, 1910, **43**, 1421) and of erythritol tetranitrate (Paulais, *Ann. pharm. Franç.*, 1945, **3**, 73).

The quantity of nitrate in the hydrolysates, after destruction of the accompanying nitrite by ammonium sulphamate, amounted to 0·8—0·9 g.-ion of nitrate per mole of tetranitrate used; thus all the nitrogen of the original tetranitrate has been accounted for. It appears that not all of the residual nitrate is in the ionic form since, in the case of methyl β-D-glucopyranoside tetranitrate, gravimetric determination of the nitrate in the form of the nitron salt as described by Baker and Easty (*loc. cit.*) gave the much lower value of 0·38 g.-ion of nitrate per mole of tetranitrate used; no methyl β-D-glucopyranoside could be detected in this hydrolysate.

The large amount of nitrite formed suggests that the hydrolysis of alkyl D-glucopyranoside tetranitrates proceeds largely by α-hydrogen elimination, *i.e.*, the E_{CO} reaction of Baker and Easty (*loc. cit.*). Substances containing carbonyl groups will be formed simultaneously and may then react with further alkali, thus accounting for the considerable consumption of alkali which occurs after hydrolysis of the original tetranitrate is substantially complete.

Experimental

Ethyl, *n*-propyl, *n*-butyl, and *n*-pentyl β-D-glucopyranoside were obtained by treating the appropriate alcohols with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of silver carbonate (Ferguson, *J. Amer. Chem. Soc.*, 1932, **54**, 4086) and hydrolysing the resulting alkyl β-D-glucopyranoside tetra-acetates by the Zemplen method. *n*-Propyl β-D-glucopyranoside was obtained crystalline; the others, being relatively difficult to crystallize, were isolated as syrups which were sufficiently pure for nitration.

Ethyl β-D-Glucopyranoside Tetranitrate.—Ethyl β-D-glucopyranoside (5 g.) was suspended in acetic anhydride (12·5 ml.) at 0° and a mixture of fuming nitric acid (10 ml.) and acetic anhydride (25 ml.), also at 0°, added fairly rapidly (Honeyman and Morgan, *Chem. and Ind.*, 1953, 1035). The nitration mixture was stirred for 1 hr. at 0° by which time all the glucoside had dissolved. The tetranitrate quickly solidified when the reaction mass was poured into a large volume of ice-water and was washed several times with cold water. The crude solid, after recrystallization from absolute ethanol (15 ml.), gave *ethyl β-D-glucopyranoside tetranitrate* as colourless needles (5·3 g.), m. p. 99—100°, $[\alpha]_D^{22}$ +6·9° (*c*, 4·4816 in $CHCl_3$) (Found: C, 25·1; H, 3·5. $C_8H_{12}O_{14}N_4$ requires C, 24·8; H, 3·1%).

n-*Propyl β-D-Glucopyranoside Tetranitrate.*—*n*-Propyl β-D-glucopyranoside (5 g.) gave n-*propyl β-D-glucopyranoside tetranitrate* (5·6 g.) which separated from absolute ethanol as colourless needles, m. p. 81—82°, $[\alpha]_D^{21}$ +6·7° (*c*, 4·0400 in $CHCl_3$) (Found: C, 26·6; H, 3·8. $C_9H_{14}O_{14}N_4$ requires C, 26·9; H, 3·5%).

n-*Butyl β-D-Glucopyranoside Tetranitrate.*—*n*-Butyl β-D-glucopyranoside (5 g.) gave the tetranitrate as a syrup (5 g.) which crystallized after several days at 0°. Recrystallization from absolute ethanol gave n-*butyl β-D-glucopyranoside tetranitrate* as colourless, slender needles (2·1 g.), m. p. 39—40°, $[\alpha]_D^{20}$ +5·4° (*c*, 3·9336 in $CHCl_3$) (Found: C, 28·5; H, 3·5. $C_{10}H_{16}O_{14}N_4$ requires C, 28·9; H, 3·8%).

n-*Pentyl β-D-Glucopyranoside Tetranitrate.*—*n*-Pentyl β-D-glucopyranoside (5 g.) gave on nitration a syrup which did not crystallize. As such a product would be unsuitable for pharmacological study it was not examined further.

The solid nitrates were not sensitive to friction, but they exploded violently when a few mg. were suddenly heated in a sealed m. p. tube.

Determination of Alkali Consumed.—To the tetranitrate (0·1—0·15 g.) dissolved in absolute methanol (20 ml.) was added 0·5N-aqueous sodium hydroxide (5 ml.). After a suitable period an aliquot portion (10 ml.) of the hydrolysate was withdrawn and the excess of alkali titrated with 0·1N-hydrochloric acid (phenolphthalein).

Determination of Nitrite.—An aliquot (1 ml.) of the hydrolysate was diluted with distilled water to 100 ml. 0·25 Ml. of the diluted material was then taken for estimation by the Griess–Ilosvay method with an " Eel " photoelectric colorimeter. 0·25 Ml. of a solution containing 0·0202 g./l. of " AnalaR " sodium nitrite was used as the standard.

Determination of Nitrate.—Nitrate was similarly determined colorimetrically by conversion into 5-nitro-2 : 4-xylenol as described by Yagoda (*Ind. Eng. Chem. Anal.*, 1943, **15**, 27). 1 Ml. of a solution containing 0·3608 g./l. of " AnalaR " potassium nitrate was used as the standard in all determinations. The validity of the method was checked with a solution containing 0·000534 g./ml. of methyl β-D-glucopyranoside tetranitrate (Found: 0·0005169, 0·0005281 g./ml.).

Determination of Nitrate in Presence of Nitrite.—To 5 ml. of a 1 : 10 dilution of the hydrolysate were added ammonium sulphamate (0·1 g.) and 2N-sulphuric acid (1 ml.). The solution was then left for 10 min. at room temperature and the nitrate in the resulting nitrite-free solution was determined colorimetrically as already described. The validity of this procedure was shown by the use of a solution containing 0·0001804 g./ml. of potassium nitrate and 0·000505 g./ml. of potassium nitrite (Found 0·0001744 g./ml. of potassium nitrate).

Solubility Determinations.—Each finely powdered tetranitrate (0·5 g.) was shaken at room temperature with distilled water (150 ml.) for 24 hr. and the resulting suspensions were equilibrated in a thermostat at 20° for a further 24 hr. Immediately before the colorimetric estimation, each suspension was filtered at 20° and a suitable volume of filtrate withdrawn. Aliquot portions (5 ml.) of methyl α- and β-D-glucopyranoside tetranitrate were used, but with the ethyl, *n*-propyl, and *n*-butyl compounds it was necessary to concentrate 100-ml. portions nearly to dryness to obtain sufficient material for colorimetric estimation.

Paper Chromatography.—The hydrolysate from methyl β-D-glucopyranoside tetranitrate was neutralized with 2N-sulphuric acid, filtered, and evaporated under reduced pressure. The resulting semi-solid mass, when dissolved in water and subjected to paper chromatography as described by Hough (*Nature*, 1950, **165**, 400), showed no trace of methyl β-D-glucopyranoside, and acid hydrolysis of the residue with boiling dilute hydrochloric acid did not give glucose.

The author acknowledges the advice and guidance of the late Principal Sir James C. Irvine, F.R.S., at whose suggestion the above work was carried out, and thanks the Wellcome Research Foundation for a grant.

DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS,
UNIVERSITY OF ST. ANDREWS MEDICAL SCHOOL, DUNDEE. [*Received, August 5th*, 1953.]

---

733. *Gladiolic Acid. Part III.* The Structures of Norisogladiolic Acid, Dihydrogladiolic Acid, and Cyclopolic Acid.*

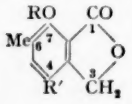
By L. A. DUNCANSON, JOHN FREDERICK GROVE, and (MRS.) J. ZEALLEY.

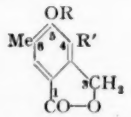
The structures of nor*iso*gladiolic acid and dihydrogladiolic acid are established as 5-hydroxy-6-methylphthalide-4-carboxylic acid (II; R = H, R′ = CO_2H) and (in the lactol form) 3-hydroxy-4-hydroxymethyl-7-methoxy-6-methylphthalide (VII*a*; R′ = Me, R″ = H) respectively. *iso*Gladiolic acid is 7-methoxy-6-methylphthalide-4-carboxylic acid (I; R = Me, R′ = CO_2H) (cf. Grove, *Biochem. J.*, 1952, **50**, 648; Brown and Newbold, *J.*, 1953, 1285). Cyclopolic acid is shown on spectroscopic evidence to be (in the lactol form) 3 : 5-dihydroxy-4-hydroxymethyl-7-methoxy-6-methylphthalide (VII*a*; R′ = Me, R″ = OH).

*iso*GLADIOLIC ACID, product of rearrangement of gladiolic acid (VI; R′ = Me, R = R″ = H) by alkali, was formulated by Grove (*Biochem. J.*, 1952, **50**, 648) as (I; R = Me, R′ = CO_2H). This structure was preferred to (II; R = Me, R′ = CO_2H) in which lactonisation had proceeded in the alternative direction because *iso*gladiolic acid was produced by oxidation under acid conditions of 4-formyl-7-methoxy-6-methylphthalide (" deoxygladiolic acid ") (I; R = Me, R′ = CHO) the structure of which was not in doubt. Nevertheless decarboxylation (with simultaneous demethylation) of *iso*gladiolic acid afforded a hydroxy-

* Part II, *Biochem. J.*, 1953, **54**, 664.

phthalide which gave no colour with ferric chloride and was considered to be (II; R = R′ = H), indicating that rearrangement had taken place at some point in the reaction sequence (I; R = Me, R′ = CHO) ⟶ *iso*gladiolic acid ⟶ (II; R = R′ = H); hence the formula (II; R = Me, R′ = CO_2H) for *iso*gladiolic acid could not entirely be excluded. A similar argument can be applied to the synthesis of *iso*gladiolic acid described by Brown and Newbold (*J.*, 1953, 1285), the final stage of which involves oxidation of (I; R = Me, R′ = CH_2·OH) to *iso*gladiolic acid under conditions very similar to those used by Grove (*loc. cit.*) for the oxidation of (I; R = Me, R′ = CHO).

(I) 



(II)

Nor*iso*gladiolic acid, obtained on demethylation of *iso*gladiolic acid with hydrobromic acid, was believed by Grove to be (I; R = H, R′ = CO_2H). A systematic study of the infra-red spectra of hydroxyphthalides (Duncanson, Grove, and Zealley, *J.*, 1953, 1331) showed that 7-hydroxyphthalides can be recognised in solution by a characteristic lowering of the phthalide >C=O stretching frequency due to intramolecular hydrogen bonding, but that a comparable lowering of frequency observed in the spectra of solidhy droxyphthalides could be caused by intermolecular hydrogen bonding. These conclusions rendered invalid the earlier orientation of nor*iso*gladiolic acid based on results obtained on a Nujol "mull"; examination of the chloroform and dioxan solution spectra of nor*iso*gladiolic acid reveals intramolecular bonding between the hydroxyl and carboxyl substituents (Table 1), the phthalide >C=O frequency occurring at the normal unbonded value (1770 $cm.^{-1}$). The characteristic >C=O frequency of a 7-hydroxyphthalide is completely absent from the solution spectra which remain unaltered after the lactone ring has been opened by treatment with alkali and the compound recovered by acidification.

Nor*iso*gladiolic acid must therefore be represented by (II; R = H, R′ = CO_2H). Methylation with diazomethane gave some methyl *iso*gladiolate, but the major product was a methyl ether methyl ester (II; R = Me, R′ = CO_2Me) not identical with methyl *iso*gladiolate. An acid-catalysed rearrangement must therefore occur during the demethylation of *iso*gladiolic acid (I; R = Me, R′ = CO_2H) since *iso*gladiolic acid gives methyl *iso*gladiolate (I; R = Me, R′ = CO_2Me) as sole product on methylation with diazomethane. Esterification of nor*iso*gladiolic acid with methanol under Fischer–Speier conditions gave approximately equal amounts of two isomeric methyl esters (II; R = H, R′ = CO_2Me) and (I; R = H, R′ = CO_2Me) oriented by their infra-red spectra (Table 1). Methylation of both esters with diazomethane gave (I; R = Me, R′ = CO_2Me) but the yield, high in the case of (I; R = H, R′ = CO_2Me), was poor with (II; R = H, R′ = CO_2Me). However, with methyl iodide each of the phenol-esters gave exclusively its own methoxy-ester, although yields were low and much starting material was recovered. Decarboxylation of nor*iso*gladiolic acid in quinoline in the presence of copper chromite gave 5-hydroxy-6-methylphthalide (II; R = R′ = H) identical with the material obtained by decarboxylation of *iso*gladiolic acid, and in low yield 7-hydroxy-6-methylphthalide (I; R = R′ = H) the structure of which was established by its infra-red spectrum characteristic of a 7-hydroxyphthalide and by methylation to the known 7-methoxy-6-methylphthalide (Brown and Newbold, *loc. cit.*). Methylation of (II; R = R′ = H) yielded 5-methoxy-6-methylphthalide identical with a synthetic specimen (Gardner and Grove, Part IV, following paper).

It is concluded that while nor*iso*gladiolic acid is best represented as 5-hydroxy-6-methylphthalide-4-carboxylic acid (II; R = H, R′ = CO_2H) in non-hydrolytic solvents, an equilibrium between (II; R = H, R′ = CO_2H) and (I; R = H, R′ = CO_2H) exists in solution under a wide variety of conditions. (I; R = Me, R′ = CO_2H and CO_2Me) are the stable configurations in the case of the methyl ether and methyl ether methyl ester of nor*iso*gladiolic acid because of steric factors attendant on the presence of the bulky methoxyl substituent; but on demethylation of *iso*gladiolic acid, rearrangement of the resulting

7-hydroxyphthalide (I; R = H, R′ = CO_2H) to the more stable salicylic acid (II; R = H, R′ = CO_2H) takes place. This rearrangement, entailing the opening and closing of a lactone ring in strongly acid solution, may be compared with similar rearrangements in the flavone and *iso*flavone series (Baker, Dunstan, Harborne, Ollis, and Winter, *Chem. and Ind.*, 1953, 277; Whalley, *ibid.*).

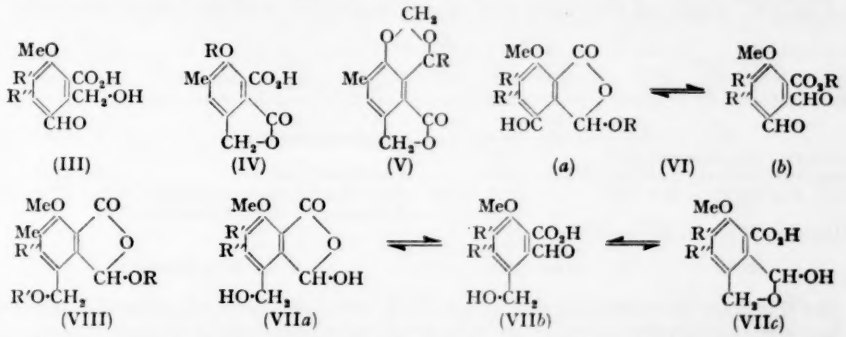
TABLE 1. >C=O *Stretching frequencies of norisogladiolic acid and derivatives in solution.*

Compound	Solvent	>C=O ($cm.^{-1}$)	Assignment
Norisogladiolic acid (II; R = H, R′ = CO_2H)	Dioxan	1770 •	Phthalide ring
		1686 •	Chelated aromatic carboxylic acid
(II; R = H, R′ = CO_2Me)	,,	1769	Phthalide ring
		1680	Chelated aromatic ester
(I; R = H, R′ = CO_2Me)	$CHCl_3$	1746	7-Hydroxyphthalide
		1719	Aromatic ester
(II; R = Me, R′ = CO_2Me)	,,	1766	Phthalide ring
		1735	Hindered aromatic ester
(I; R = Me, R′ = CO_2Me)	,,	1766	Phthalide ring
		1717	Aromatic ester
5-Hydroxy-6-methylphthalide (II; R = R′ = H) ...	Dioxan	1769	Phthalide ring
7-Hydroxy-6-methylphthalide (I; R = R′ = H) ...	$CHCl_3$	1736	7-Hydroxyphthalide
5-Methoxy-6-methylphthalide (II; R = Me, R′ = H)	,,	1757	Phthalide ring
7-Methoxy-6-methylphthalide (I; R = Me, R′ = H)	,,	1761	Phthalide ring

• 1763 and 1682 $cm.^{-1}$ respectively in $CHCl_3$.

Dihydrogladiolic acid $C_{11}H_{12}O_5$ was believed to be (III; R′ = Me, R″ = H) since it was converted into 4-formyl-7-methoxy-6-methylphthalide (I; R = Me, R′ = CHO) above its melting point *in vacuo* (Raistrick and Ross, *Biochem. J.*, 1952, **50**, 635), or by boiling dilute mineral acids (Grove, *loc. cit.*); and Clemmensen reduction gave 7-methoxy-4 : 6-dimethylphthalide (I; R = R′ = Me). Further work has shown that (III; R′ = Me, R″ = H) does not account satisfactorily either for the chemistry of dihydrogladiolic acid or for its infra-red spectrum in solution.

Raistrick and Ross showed that acetylation of dihydrogladiolic acid with acetic anhydride–pyridine gave a neutral acetyl derivative (" dihydrogladiolide diacetate ") which they formulated as [I; R = Me, R′ = $CH(OAc)_2$], but all attempts to prepare this derivative from (I; R = Me, R′ = CHO) by an identical acetylation procedure or by a variety of other methods have proved unsuccessful. Secondly, whereas dihydrogladiolic acid is recovered unchanged on acidification after 18 hours in 2N-sodium hydroxide at room temperature or after being heated at 100° in 0·1N-sodium hydroxide, (I; R = Me, R′ = CHO) is also recovered unchanged after similar treatment; the alkaline solutions of (I; R = Me, R′ = CHO) should be equivalent to those of (III; R′ = Me, R″ = H)



because back-titration shows the phthalide ring to have been opened under these conditions. Thirdly, by oxidation of dihydrogladiolic acid with alkaline iodine or alkaline hydrogen peroxide, Raistrick and Ross obtained a phthalidecarboxylic acid isomeric with *iso*gladiolic acid; in the present investigation demethylation of this compound gave 6-hydroxy-5-methylphthalide-7-carboxylic acid (IV; R = H) which yields the original oxidation

product on methylation. We have synthesised (IV; R = H) by hydrolysis of (V; R = O) prepared by the method of Charlesworth, Anderson, and Thompson (*Canad. J. Res.*, 1953, *B*, **31**, 65) in which (V; R = H_2) obtained by the action of formaldehyde and hydrochloric acid on 2-hydroxy-*p*-toluic acid was oxidised by chromic oxide. Decarboxylation of (IV; R = H) gave the known 6-hydroxy-5-methylphthalide. The dihydrogladiolic acid oxidation product must therefore be 6-methoxy-5-methylphthalide-7-carboxylic acid (IV; R = Me) and it is not easy to see how this can arise from (III; R′ = Me, R″ = H), particularly as dihydrogladiolic acid is known not to undergo rearrangement under the mild alkaline conditions employed.

A comprehensive study of the oxidation of (I; R = Me, R′ = CHO) and dihydrogladiolic acid in parallel experiments with a wide variety of conditions and oxidising agents has shown that, while (I; R = Me, R′ = CHO) always gives *iso*gladiolic acid as the initial product, dihydrogladiolic acid gives (IV; R = Me) under alkaline, but gladiolic acid (VI; R′ = Me, R = R″ = H) under acid conditions.

These results are best explained on the basis of structure (VII; R′ = Me, R″ = H) for dihydrogladiolic acid. In acid solution where the lactol form (VII*a*; R′ = Me, R″ = H) is the predominant molecular species the hydroxymethyl substituent is the most sensitive to oxidative attack and gladiolic acid is the initial product; in alkaline solution the formyl substituent in the open form (VII*b*; R′ = Me, R″ = H) is attacked first, with the production of (IV; R = Me). Strong independent support for structure (VII; R′ = Me, R″ = H) for dihydrogladiolic acid comes from the infra-red spectrum of a dioxan solution (Table 2) which shows >C=O absorption at 1774 $cm.^{-1}$ characteristic of the presence of a phthalide ring and consistent only with (VII*a*; R′ = Me, R″ = H).

Final proof of the structure of dihydrogladiolic acid was obtained as follows. Catalytic reduction of the neutral monoacetyl derivative of gladiolic acid (VI*a*; R = Ac, R′ = Me, R″ = H) gave (VIII; R = Ac, R′ = R″ = H) which retained the characteristic lactol acetate infra-red absorption (bands close to 1780 and 1770 $cm.^{-1}$; Table 2). Mild alkaline hydrolysis of this compound under conditions where dihydrogladiolic acid is known to be stable gave dihydrogladiolic acid.

Acetylation of (VIII; R = Ac, R′ = R″ = H) gave a neutral acetyl derivative identical with "dihydrogladiolide diacetate" which must therefore have the structure (VIII; R = R′ = Ac; R″ = H). The infra-red spectrum of this derivative (Table 2) showed a typical ester >C=O absorption band close to 1740 $cm.^{-1}$ consistent with that structure, but incompatible with [I; R = Me, R′ = $CH(OAc)_2$], since compounds containing the $CH(OAc)_2$ grouping, *e.g.*, 3-acetoxy-4-diacetoxymethyl-7-methoxy-6-methylphthalide, show >C=O absorption close to 1780 $cm.^{-1}$.

TABLE 2. *Infra-red absorption data for dihydrogladiolic acid and related compounds.*

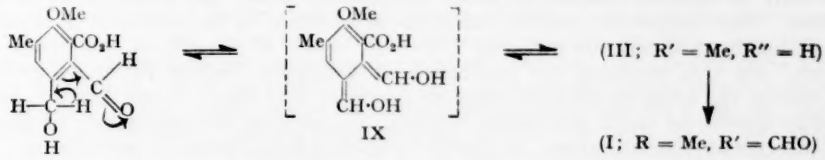
Compound	>C=O $CHCl_3$	>C=O Solid	-OH Solid
(VI*a*; R = Ac, R′ = Me, R″ = H)	1786	—	—
	—	1768	—
	1775	—	—
	1700	1700	—
3-Acetoxy-4-diacetoxymethyl-7-methoxy-6-methylphthalide	—	1785	—
	1776	1765	—
(VIII; R = Ac, R′ = R″ = H)	—	1776	3490
	—	1764	—
(VIII; R = R′ = Ac, R″ = H)	1786	1796	—
	1776	1770	—
	1744	1737	—
"Cyclopolide triacetate" (VIII; R = R′ = Ac, R″ = OAc)	—	1786	—
	—	1772	—
	—	1740	—
Dihydrogladiolic acid	1774	1722	3340, 3240
Cyclopolic acid	1768*	1700	—
6-Hydroxy-5-methylphthalide	1756	1734	3280
6-Methoxy-5-methylphthalide	1757	—	—

* In dioxan.

[At this point we were informed by Dr. G. T. Newbold (personal communication) that he had obtained similar results and reached similar conclusions in a series of compounds derived from 3-formylopianic acid (VI; R = H, R′ = R″ = OMe) and we agreed to the simultaneous publication of our findings. See Brown and Newbold, *J.*, 1953, 1285.]

The formation of (I; R = Me, R′ = CHO) from dihydrogladiolic acid (see above) involves a novel type of molecular rearrangement resulting in the interchange of the formyl and hydroxymethyl substituents. Although the precise mechanism has not been deter-

mined we believe that prototropic rearrangement of (VII*b*; R′ = Me, R″ = H) (present in trace amounts even under acid conditions) can afford the hypothetical intermediate (IX) [its formation in the melt may involve the simultaneous acquisition and release of protons between 2 molecules of (VII*b*)] which under conditions favouring the formation of a stable phthalide ring gives (I; R = Me, R′ = CHO) *via* (III; R′ = Me, R″ = H).



The formation of 7-methoxy-4 : 6-dimethylphthalide on Clemmensen reduction of dihydrogladiolic acid is explained on the basis of rearrangement to (I; R = Me, R′ = CHO) before the reduction of the formyl group.

Although there is no evidence for a true equilibrium between (VII; R′ = Me, R″ = H) and (III; R′ = Me, R″ = H) in solution at room temperature, as shown by the spectroscopic evidence and the results of the oxidation experiments described above, dihydrogladiolic acid shows keto–lactol tautomerism in aqueous solution and an equilibrium exists between the lactol (VII*a*; R′ = Me, R″ = H) and open-chain (VII*b*; R′ = Me, R″ = H) forms, the pH being the determining factor as in the case of gladiolic acid (Grove, *J.*, 1952, 3345; *idem*, *Biochem. J.*, 1953, **54** 664).

The ultra-violet absorption (Table 3) in buffer solution of pH 2·9 resembles those of a chloroform solution and of 3-acetoxy-4-diacetoxymethyl-7-methoxy-6-methylphthalide (max. at 297 mμ; log ε 3·73) and indicates the presence of the lactol form (VII*a*; R′ = Me, R″ = H). In alkaline solution the ultra-violet absorption of the open-chain anion is close to that of gladiolic acid (max. at 276 mμ; log ε 3·08) and resembles that of a 2 : 6-disubstituted benzoic acid. The typical absorption of the conjugated benzenoid and carbonyl chromophores is not observed; this may be due to steric factors or to hydration of the formyl substituent either by reaction with the medium or intramolecularly (VII*c*; R′ = Me, R″ = H) (Lüttke, *Chem. Ber.*, 1950, **83**, 571; Hurd and Saunders, *J. Amer. Chem. Soc.*, 1952, **74**, 5324). In ethanol solution the ultra-violet absorption of dihydrogladiolic acid was found to vary with concentration. Thus a $4{\cdot}91 \times 10^{-3}$M-solution showed $\lambda_{max.}$ 296 mμ (log ε 3·42) and a $2{\cdot}19 \times 10^{-4}$M-solution $\lambda_{max.}$ 276 mμ (log ε 3·31). This phenomenon is due to dissociation of dihydrogladiolic acid in ethanol, the more dilute solution containing a high proportion of anion.

The formulation of dihydrogladiolic acid as (VII; R′ = Me, R″ = H) suggested that the closely related metabolic product of *Penicillium cyclopium*, cyclopolic acid, might have the structure (VII; R′ = Me, R″ = OH) rather than (III; R′ = Me, R″ = OH) proposed by Birkinshaw, Raistrick, Ross, and Stickings (*Biochem. J.*, 1952, **50**, 610). Strong support for this view comes from the infra-red spectrum of cyclopolic acid in dioxan which

TABLE 3. *Ultra-violet absorption data for dihydrogladiolic acid.*

Solvent	$\lambda_{max.}$ (mμ)	log ε
Chloroform	299	3·43
McIlvaine buffer pH 2·9	297	3·31
,, ,, pH 4·0	286—292	3·17
,, ,, pH 5·0	277	3·21
0·1N-Sodium hydroxide	277	3·26

shows phthalide ring C=O absorption at 1768 cm.$^{-1}$, consistent only with (VII*a*; R′ = Me, R″ = OH). No bands which can be attributed to the —CO_2H group are observed. Moreover, while cyclopaldic acid (VI; R = H, R″ = OH) gives a green colour in methanol with the titanous chloride reagent of Weygand and Csendes (*Chem. Ber.*, 1952, **85**, 45), similar to that given by salicylaldehyde, cyclopolic acid gives no colour with this reagent. In addition, Birkinshaw *et al.* observed that, while cyclopaldic acid in common with most *o*-hydroxy-aldehydes gave a yellow solution in sodium hydroxide, cyclopolic acid formed a

colourless solution. In view of these observations, which favour (VII; R′ = Me, R″ = OH) the intense purple ferric reaction of cyclopolic acid which is replaced by an orange colour in the thiosemicarbazone, the conductometric titration of cyclopolic acid as a dibasic acid and the resistance shown by cyclopolic acid towards oxidation by alkaline hydrogen peroxide are surprising and might be taken to indicate an equilibrium with (III; R′ = Me, R″ = OH) in aqueous solution at room temperature under the influence of certain reagents. Nevertheless we consider the infra-red evidence to be conclusive in showing that cyclopolic acid has the structure (VII; R′ = Me, R″ = OH) in non-hydrolytic solvents. On this structure the production of 4-hydroxy-7-iodo-6-methoxy-5-methylphthalide by the action of alkaline iodine on cyclopolic acid (Ross, Thesis, London, 1951) is readily understood and it is no longer necessary to postulate the intermediate formation and subsequent rearrangement of 3-iodo-4-methoxy-5-methylphthalaldehyde in this reaction. The formation of cyclopolide, 4-formyl-5-hydroxy-7-methoxy-6-methylphthalide, when cyclopolic acid is boiled with dilute mineral acids, and of 5 : 7-dimethoxy-4 : 6-dimethylphthalide on Clemmensen reduction of the acid followed by methylation, has then to be explained on the basis of a molecular rearrangement in acid solution similar to that postulated for dihydrogladiolic acid. The triacetyl derivative of cyclopolic acid, formulated by Birkinshaw *et al.* as a derivative of cyclopolide, resembles (VIII; R = R′ = Ac, R″ = H) in showing ester >C=O absorption at 1740 cm.$^{-1}$ (Table 2) and is therefore more correctly represented by (VIII; R = R′ = Ac, R″ = OAc).

Experimental

M. p.s are corrected. Microanalyses are by Messrs. W. Brown and A. G. Olney. Infra-red spectra were measured with a Grubb–Parsons S 3A spectrometer through which dry air was continuously circulated. Ultra-violet spectra were measured using a Unicam S.P. 500 spectrophotometer and 1-cm. path-length, except for ethanol solutions of dihydrogladiolic acid where the Hilger medium quartz spectrograph was used (path-length 0·1—1 cm.). B.D.H. "Spectroscopic ethanol" was used in these experiments. Comparison of the infra-red spectra was used to check identifications by mixed m. p. determination in all cases of suspected identity.

Pure specimens of cyclopolic acid, m. p. 147—148° (decomp.), and cyclopaldic acid, m. p. 224—225°, were kindly provided by Prof. H. Raistrick, F.R.S. Acetylation of cyclopolic acid with acetic anhydride–pyridine gave the triacetyl derivative ("cyclopolide triacetate") (VIII; R = R′ = Ac, R″ = OAc), m. p. 114°.

Dihydogladiolic acid (VII; R′ = Me, R″ = H) was obtained only in very low and variable yield by extraction of cultures of *Penicillium gladioli* McCull and Thom (N.C.T.C., 3994) and formed colourless prisms, m. p. 135—136° (decomp.), from ethyl acetate–benzene (Raistrick and Ross, *loc. cit.*) (Found: C, 59·0; H, 5·3. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%).

After 18 hr. in 2N-sodium hydroxide at room temperature, or after 45 min. at 100° with 0·1N-sodium hydroxide, dihydrogladiolic acid was precipitated unchanged on acidification of the cooled solutions with hydrochloric acid. Dihydrogladiolic acid underwent degradation with the formation of both neutral and acidic material under reflux (1 hr.) with 2N-sodium hydroxide. Acetylation of dihydrogladiolic acid with acetic anhydride–pyridine according to Raistrick and Ross (*loc. cit.*) gave colourless needles, m. p. 70°, of "dihydrogladiolide diacetate" identical with (VIII; R = R′ = Ac, R″ = H).

Dihydrogladiolic acid (3·0 mg.) dissolved in 2N-hydrochloric acid (0·3 ml.) at 100°. After a few minutes colourless needles began to separate from the slightly yellow solution and after 15 min. these were filtered off (2·5 mg.) and identified as (I; R = Me, R′ = CHO).

4-Formyl-7-methoxy-6-methylphthalide (I; R = Me, R′ = CHO), m. p. 173°, was prepared by reduction of gladiolic acid (Grove, *loc. cit.*). Careful acidification of the alkaline solutions obtained by heating (I; R = Me, R′ = CHO) with excess of 0·1N-sodium hydroxide at 100° for 45 min. precipitated (I; R = Me, R′ = CHO) unchanged. This treatment with alkali has previously been shown to open the phthalide ring of (I; R = Me, R′ = CHO). It was also recovered unchanged after 2 days at room temperature in acetic anhydride–pyridine, treatment with acetic anhydride and concentrated sulphuric acid (1 drop), and heating at 100° for 4 hr. with acetic anhydride and acetic acid (cf. acetylation of gladiolic acid; Grove, *loc. cit.*). Clemmensen reduction of (I; R = Me, R′ = CHO) as described for gladiolic acid gave needles, m. p. 112°, identical with 7-methoxy-4 : 6-dimethylphthalide.

3-Acetoxy-4-hydroxymethyl-7-methoxy-6-methylphthalide (VIII; R = Ac, R′ = R″ = H).—3-Acetoxy-4-formyl-7-methoxy-6-methylphthalide (80 mg.), in ethanol (10 ml.), was added to a reduced platinum oxide catalyst (15 mg.), in ethanol (5 ml.), and the hydrogenation carried out at 16°. Rapid uptake of 1 mol. (10 min.) was followed by a slower uptake of a second mol. (1 hr.). Reduction was stopped, the catalyst filtered off, and the solvent removed. Crystallisation of the crude product from ethanol (0·7 ml.) furnished unchanged starting material (23 mg.; m. p. 139°). Dilution of the filtrate to 2 ml. with water yielded a further small fraction of impure starting material (2 mg.; m. p. 130—136°), and the aqueous-ethanolic filtrate was then made alkaline with sodium hydrogen carbonate and extracted with ether. Acidification of the aqueous layer and recovery yielded a gummy acid (10 mg.). The neutral ethereal extract furnished a gum which after two crystallisations from benzene–light petroleum (b. p. 60—80°) gave *3-acetoxy-4-hydroxymethyl-7-methoxy-6-methylphthalide*, needles (16 mg.), m. p. 85° (Found: C, 58·55; H, 5·5. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%). Acetic anhydride–pyridine at 20° gave the *acetyl* derivative (VIII; R = R′ = Ac, R″ = H), colourless needles (from methanol), m. p. 70° (Found: C, 58·5; H, 5·4. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2%).

Hydrolysis of (VIII; R = Ac, R′ = R″ = H).—The compound (3·1 mg.) dissolved when kept in 2N-sodium hydroxide (0·1 ml.). After 4 hr. at room temperature acidification with concentrated hydrochloric acid precipitated dihydrogladiolic acid as needles (2·2 mg.), m. p. 132°.

Oxidation Experiments with (a) *Dihydrogladiolic Acid and* (b) *4-Formyl-7-methoxy-6-methylphthalide* (I; R = Me, R′ = CHO).—(A) *Alkaline hydrogen peroxide.* (*a*) Dihydrogladiolic acid yielded 6-methoxy-5-methylphthalide-7-carboxylic acid (IV; R = Me), m. p. 216°, identical with the phthalidecarboxylic acid obtained by Raistrick and Ross (*loc. cit.*). When (IV; R = Me) was heated at 100° for 20 min. with hydrobromic acid (*d* 1·25) colourless needles of *6-hydroxy-5-methylphthalide-7-carboxylic acid*, m. p. 198°, identical with a synthetic specimen, separated (Found: C, 57·7; H, 4·0. $C_{10}H_8O_5$ requires C, 57·7; H, 3·9%).

(*b*) The phthalide (I; R = Me, R′ = CHO) (27·4 mg.) was dissolved in 0·108N-sodium hydroxide (4·05 ml.) at 100° (45 min.) and then hydrogen peroxide (20-vol.; 2 ml.) was added to the cooled solution. After 24 hr. an additional 1 ml. of hydrogen peroxide was added and the mixture set aside for a further 24 hr. Back-titration with 0·115N-hydrochloric acid used up 1·41 ml., whence the acidity liberated during solution and oxidation ≡ 2·53 ml. of 0·108N-sodium hydroxide (Calc. for 2 equiv., 2·46 ml.). The solution was made strongly acid and after 4 hr. at 0° the precipitated solid was dissolved in ether and the ethereal solution extracted with sodium hydrogen carbonate solution. Acidification of the carbonate extract, ether-extraction, and recovery yielded 7-methoxy-6-methylphthalide-4-carboxylic acid (I; R = Me, R′ = CO_2H) (m. p. 200—230°), crystallising from water in needles (10·6 mg.), m. p. 234°.

(B) *Alkaline iodine.* (*a*) Dihydrogladiolic acid (42·8 mg.) yielded (IV; R = Me) (12·2 mg.) (Raistrick and Ross, *loc. cit.*).

(*b*) The phthalide (I; R = Me, R′ = CHO) (27·0 mg.) in warm methanol (3 ml.) was treated with 0·108N-sodium hydroxide (15·0 ml.) and 0·1N-iodine (10·0 ml.) and kept for 18 hr. at room temperature. Back-titration with 0·1N-sodium thiosulphate after addition of excess of hydrochloric acid showed the iodine consumed to be equivalent to 1·01 atoms of oxygen. Extraction of the acid solution with ethyl acetate and recovery furnished (I; R = Me, R′ = CO_2H) (10·0 mg.), m. p. 236°.

(C) *Chromic oxide.* (*a*) Dihydrogladiolic acid (17 mg.) in acetic acid (2 ml.) was treated with chromic oxide (12 mg.) in water (0·5 ml.). After 12 hr. the clear solution was diluted with water and extracted with chloroform, furnishing a gum which was sublimed at 160°/10^{-2} mm. Crystallisation of the sublimate from water gave gladiolic acid, m. p. 158—160° (4·5 mg.).

(*b*) On oxidation of (I; R = Me, R′ = CHO) (20 mg.) under identical conditions, needles (5 mg.) of (I; R = Me, R′ = CO_2H), m. p. 234°, had crystallised from the mixture after 12 hr. On dilution with water the filtrate deposited a further 5 mg. of (I; R = Me, R′ = CO_2H).

(D) *Acid potassium permanganate.* (*a*) Dihydrogladiolic acid (20 mg.) in 2N-sulphuric acid (3 ml.) at 90° was oxidised by rapid addition of potassium permanganate (15 mg.) in water. The solid product (5 mg.), m. p. 140—150°, which separated on cooling gave the green colour with ammonia solution (*d* 0·880) characteristic of gladiolic acid, but resisted further purification. Extraction of the filtrate with ether and recovery furnished a semi-solid mass (11 mg.) from which needles of gladiolic acid (6 mg.), m. p. 154°, were obtained by crystallisation from water.

(*b*) The phthalide (I; R = Me, R′ = CHO) furnished (I; R = Me, R′ = CO_2H) as described by Grove (*loc. cit.*).

(E) *Acid hydrogen peroxide.* (*a*) Dihydrogladiolic acid (10 mg.) was kept in glacial acetic acid (1 ml.) and hydrogen peroxide (20-vol; 1·5 ml.) for 24 hr. at room temperature. Dilution

with water and extraction with chloroform afforded a gum which gave a colourless sublimate at 160—180°/10^{-2} mm. Separation of the sublimate into neutral and acidic fractions by dissolution in ether and extraction with sodium hydrogen carbonate furnished (I; R = Me, R′ = CHO) (1·5 mg.) and gladiolic acid (1·1 mg.).

6-Hydroxy-5-methylphthalide.—6-Methoxy-5-methylphthalide (120 mg.) (Charlesworth, Rennie, Sinder, and Yan, *Canad. J. Res.*, 1945, *B*, **23**, 17) was heated under reflux for 5 min. with hydrobromic acid (3 ml.; *d* 1·25), and the solution was diluted with water (10 ml.) and extracted with ether. The ethereal solution was extracted with 2N-sodium hydroxide; on acidification with concentrated hydrochloric acid a little amorphous material separated and was filtered off and discarded, and the clear filtrate extracted with ether. The crude product (75 mg.; m. p. 190—200°) crystallised from ethyl acetate in needles, m. p. 210° (Found: C, 65·9; H, 4·9. Calc. for $C_9H_8O_3$: C, 65·85; H, 4·9%). Charlesworth *et al.* (*loc. cit.*, 1953) give m. p. 205°.

6-Hydroxy-5-methylphthalide-7-carboxylic Acid (IV; R = H).—The lactone (V; R = O) of 6-hydroxymethyl-8-methyl-4-oxobenzo-1 : 3-dioxan-5-carboxylic acid (Charlesworth, Anderson, and Thompson, *loc. cit.*) was hydrolysed quantitatively by 3N-sodium hydroxide under reflux in 1·5 hr. Acidification and crystallisation from water gave *6-hydroxy-5-methylphthalide-7-carboxylic acid*, needles, m. p. 198° [Found: C, 57·7; H, 3·9%; *M* (Rast), 238. $C_{10}H_8O_5$ requires C, 57·7; H, 3·9%; *M*, 208]. Methylation with methyl sulphate in 10% sodium hydroxide, followed by warming for 1 hr. on a steam-bath with sodium hydroxide to hydrolyse any methyl ester formed, gave 6-methoxy-5-methylphthalide-7-carboxylic acid (IV; R = Me), m. p. 214°, identical with the product of oxidation of dihydrogladiolic acid by alkaline hydrogen peroxide.

The acid (IV; R = H) was decarboxylated by quinoline with a copper chromite catalyst at 175—190° (2½ hr.) as described for (II; R = H, R′ = CO_2H) (see below) and the product worked up similarly. Carbon dioxide corresponding to 1·08 mols. was collected. Sublimation of the product and crystallisation from water gave 6-hydroxy-5-methylphthalide.

5-Hydroxy-6-methylphthalide-4-carboxylic Acid (*Norisogladiolic Acid*) (II; R = H, R′ = CO_2H).—The specimen prepared previously (Grove, *loc. cit.*) melted at 254—256° (decomp.). Specimens prepared later by the same method have melted at 276° (decomp.) under the same conditions, but no significant differences in analysis or infra-red spectra (in Nujol "mull" or in dioxan solution) have been detected. Grinding the higher-melting material lowered the m. p. to 268° (decomp.), and it appears that the m. p. depends on the particle size. The yield, m. p., and infra-red spectrum of the product were unaltered when the time of heating *iso*-gladiolic acid with hydrobromic acid was reduced to 10 min. The acid (II; R = H, R′ = CO_2H) (49 mg.) was heated on the steam-bath for 1 hr. with an excess of 0·1N-sodium hydroxide. Back-titration with 0·1N-hydrochloric acid gave equiv. 104 [Calc. for $C_{10}H_8O_5$: equiv., 104 (dibasic acid)]. Acidification to Congo-red precipitated colourless needles (47 mg.), m. p. 268° (decomp.) raised to 274° (decomp.) by crystallisation from ethanol. The infra-red spectrum was identical with that of the starting material and the mixed m. p. showed no depression.

Methyl 7-Methoxy-6-methylphthalide-4-carboxylate (*Methyl* iso*Gladiolate*) (I; R = Me, R′ = CO_2Me).—*iso*Gladiolic acid and ethereal diazomethane in the presence of methanol gave a homogeneous colourless solid, m. p. 136—138°. Recrystallisation from methanol gave needles, m. p. 142—143°, identical with methyl *iso*gladiolate prepared under Fischer–Speier conditions (Grove, *loc. cit.*). The ester showed dimorphism. The two forms had the same m. p. and appearance, and the same infra-red spectra in chloroform solution, but different infra-red spectra in the solid state. Form A, usually obtained by the Fischer–Speier method from (I; R = Me, R′ = CO_2H) showed bands at 1773 s, 1705 s, 1602 m, 1499 m, 1330 s, 1313 m, 1283 m, 1247 s, 1217 s, 1196 w, 1175 m, 1159 w, 1107 s, 1028 m, 1002 s, 967 m, 935 w, 909 m, 880 w, 797 m, 780 m, 767 w, 729 w. Form B, generally obtained by methylation of (II; R = H, R′ = CO_2H) showed bands at 1771 s, 1736 s, 1618 m, 1593 m, 1496 m, 1310 s, 1275 m, 1241 m, 1208 s, 1188 m, 1111 m, 1101 m, 1086 s, 1022 s, 1001 s, 958 m, 939 w, 913 w, 880 w, 796 m, 775 w, 769 w, 730 w. Forms A and B were interconvertible by seeding of methanol solutions with the appropriate crystalline modification.

Decarboxylation of (II; R = H, R′ = CO_2H).—The acid (0·79 g.) was decarboxylated in quinoline at 180° in the presence of copper chromite, and the products were worked up as described by Grove (*loc. cit.*). Ether-extraction of the acidified filtrate yielded a brown solid (*ca.* 0·4 g.). Sublimation at room temperature and 10^{-2} mm. gave an oil which did not solidify. At 80—100°/10^{-4} mm. an orange solid (28 mg.) was obtained which on recrystallisation from methanol formed colourless needles of *7-hydroxy-6-methylphthalide* (I; R = R′ = H), m. p. 127° (Found: C, 65·7; H, 5·1. $C_9H_8O_3$ requires C, 65·85; H, 4·9%). It gave an intense blue

colour with ferric chloride in ethanol. With ethereal diazomethane in the presence of methanol it gave needles, m. p. 118°, identical with 7-methoxy-6-methylphthalide (I; R = Me, R′ = H) kindly supplied by Dr. G. T. Newbold.

The unsublimed material (321 mg.) crystallised from ethanol as brown needles, m. p. 235°, purified by sublimation at 160—180°/10^{-5} mm. followed by recrystallisation from ethanol, giving colourless needles, m. p. 244°, of 5-hydroxy-6-methylphthalide (II; R = R′ = H) identical with a specimen obtained by decarboxylation (and simultaneous demethylation) of *iso*gladiolic acid. The infra-red spectrum was distinct from that of 6-hydroxy-5-methylphthalide. With ethereal diazomethane (II; R = R′ = H) gave colourless needles (from water), m. p. 144°, identical with a synthetic specimen of 5-methoxy-6-methylphthalide (Gardner and Grove, Part IV, following paper).

Methylation of (II; R = H, R′ = CO_2H).—(a) *With diazomethane.* The acid (100 mg.) in methanol was kept with excess of ethereal diazomethane for 2 days at room temperature. Fractional crystallisation of the crude product from methanol yielded (I; R = Me, R′ = CO_2Me) (30 mg.), m. p. 142°, and *methyl 5-methoxy-6-methylphthalide-4-carboxylate* (II; R = Me, R′ = CO_2Me), colourless needles, m. p. 132° (53 mg.) (Found: C, 61·0; H, 5·4. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%). The infra-red spectrum of this compound both in the solid state and in solution differed from (I; R = Me, R′ = CO_2Me) (both forms A and B), and a mixed m. p. determination with (I; R = Me, R′ = CO_2Me) showed a 15° depression.

(b) *With methanolic hydrogen chloride.* The acid (75 mg.), heated under reflux for 2 hr. with methanol (30 ml.) containing 10% of hydrogen chloride, yielded a mixture, separated by chromatography of its benzene solution on a short column of neutral alumina activated at 180°. (i) Elution with benzene and crystallisation from methanol gave colourless needles (36 mg.) of *methyl 5-hydroxy-6-methylphthalide-4-carboxylate* (II; R = H, R′ = CO_2Me), m. p. 212° (Found: C, 59·1; H, 4·75. $C_{11}H_{10}O_5$ requires C, 59·45; H, 4·5%). It gave a reddish-purple colour in ethanol with ferric chloride. The ester (20 mg.) in methanol (4 ml.), treated for 1 day at 20° with excess of ethereal diazomethane, gave (I; R = Me, R′ = CO_2Me) (9 mg.), m. p. 142° after three crystallisations from methanol. The mother-liquors contained a solid (8 mg.), m. p. 120—138°, which resisted purification by fractional crystallisation. The ester (II; R = H, R′ = CO_2Me) (28 mg.), acetone (5 ml.), potassium carbonate (0·2 g.) and methyl iodide (0·2 ml.) were heated under reflux for 3 hr. Water (5 ml.) was added and the solution extracted with ether. Removal of the solvent and recrystallisation of the residue (8 mg.) gave (II; R = Me, R′ = CO_2Me), m. p. 128°. Acidification of the aqueous layer precipitated starting material (14 mg.). No improvement in yield was obtained by using a larger excess of methyl iodide and heating for 8·5 hr.

(ii) Elution of the more strongly adsorbed material with benzene and 1% of methanol, followed by crystallisation from benzene or methanol, gave colourless prisms (24 mg.) of *methyl 7-hydroxy-6-methylphthalide-4-carboxylate* (I; R = H, R′ = CO_2Me), m. p. 197° (Found: C, 59·8; H, 4·8. $C_{11}H_{10}O_5$ requires C, 59·45; H, 4·5%). It gave an intense purple colour in ethanol with ferric chloride. The ester (20 mg.) in methanol (5 ml.), treated for 2 days at 20° with excess of ethereal diazomethane, gave (I; R = Me, R′ = CO_2Me) (16 mg.), m. p. 142°, on concentration of the solvent. The ester (I; R = H, R′ = CO_2Me) (25 mg.), potassium carbonate (0·2 g.), acetone (5 ml.), and methyl iodide (0·2 ml.) were heated under reflux for 8·5 hr. The acetone was removed *in vacuo*, water (8 ml.) was added, and the mixture shaken for 10 min. The residual solid (5 mg.) was collected and recrystallised from methanol, to give (I; R = Me, R′ = CO_2Me), m. p. 144°. Acidification of the filtrate, extraction with ether, and recovery gave starting material (13 mg.)

We are indebted to the Dept. of Microbiology in these laboratories for supplying the specimen of dihydrogladiolic acid, to Messrs. B. Akehurst and D. Gardner for technical assistance, and to Dr. G. T. Newbold and Prof. H. Raistrick, F.R.S., for their helpful co-operation.

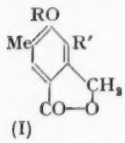
Imperial Chemical Industries Limited, Butterwick Research Laboratories,
The Frythe, Welwyn, Herts. [*Received, July 15th,* 1953.]

734. *Gladiolic Acid. Part IV.* Synthesis of 5-Methoxy-6-methylphthalide.*

By D. Gardner and John Frederick Grove.

The synthesis is described of 5-methoxy-6-methylphthalide, the methyl ether of a degradation product of gladiolic acid (Grove, *Biochem. J.*, 1952, **50**, 648).

The hydroxy-methyl-phthalide, m. p. 244°, obtained by decarboxylation of *iso*gladiolic acid (Grove, *Biochem. J.*, 1952, **50**, 648) and nor*iso*gladiolic acid (I; R = H, R′ = CO_2H) (Duncanson, Grove, and Zealley*) has now been shown to be 5-hydroxy-6-methylphthalide (I; R = R′ = H) by synthesis of the methyl ether. The method of synthesis is essentially that devised by Brown and Newbold (*J.*, 1953, 1285) for 7-methoxy-6-methylphthalide, and required as intermediate 5-hydroxy-2-nitro-*p*-toluic acid.†



(I)

Nitration of 3-hydroxy-*p*-toluic acid (Borsche and Böcker, *Ber.*, 1903, **36**, 4357) gives the 2 : 6-dinitro-compound, even under mild conditions and mononitration of 3-methoxy-*p*-toluic acid gives exclusively the 2-nitro-derivative (Simonsen and Rau, *J.*, 1921, **119**, 1339). However, by nitration of 3-hydroxy-*p*-tolunitrile Borsche and Böcker obtained two mononitro-compounds, m. p. 141—142° and 191—193°, believed to be the 3-hydroxy-2-nitro- and 5-hydroxy-2-nitro-*p*-tolunitrile respectively although their structures were not firmly established.

In the present investigation, nitration of 3-hydroxy-*p*-tolunitrile gave a mixture of two nitro-compounds, m. p. 144—145° and 210—211° respectively, whose orientation was established by hydrolysis to the corresponding toluic acids, the lower-melting isomer giving 3-hydroxy-2-nitro-*p*-toluic acid previously obtained by demethylation of its methyl ether, whose structure was proved by Simonsen and Rau. Catalytic reduction of 5-methoxy-2-nitro-*p*-toluic acid yielded the corresponding amine which furnished 2-amino-5-methoxy-4-methylbenzyl alcohol on further reduction with lithium aluminium hydride. Diazotisation, treatment with cuprous cyanide, and hydrolysis, without isolation of the intermediate nitrile, then gave the desired phthalide (I; R = Me, R′ = H).

Experimental

M. p.s are corrected. Microanalyses are by Messrs. W. Brown and A. G. Olney.

Nitration of 3-*Hydroxy*-p-*toluic Acid.*—The acid (1 g.) was added to nitric acid (*d* 1·42) as described below for 3-hydroxy-*p*-tolunitrile. Crystallisation of the product from ethanol furnished yellow needles, m. p. 215°, of 3-hydroxy-2 : 6-dinitro-*p*-toluic acid, identical (mixed m. p.) with a specimen prepared according to Borsche and Böcker's method (*loc. cit.*) (Borsche and Böcker give m. p. 200°) (Found: C, 39·7; H, 2·5; N, 11·6. Calc. for $C_8H_6O_7N_2$: C, 39·7; H, 2·5; N, 11·6%).

Nitration of 3-*Hydroxy*-p-*tolunitrile.*—The nitrile, m. p. 99° (1 g.; Borsche and Böcker, *loc. cit.*) was added in portions to nitric acid (*d* 1·42; 2 g.) at −5° with vigorous stirring. After 10 min. the mixture was poured over cracked ice (20 g.), and the solid collected and crystallised from ethanol, giving the fractions (i), m. p. 142—145° (370 mg.), (ii) m. p. 130—180° (140 mg.), (iii) m. p. 190—195° (280 mg.), and (iv) gum. Recrystallisation of (i) and (ii) from ethanol furnished *3-hydroxy-2-nitro*-p-*tolunitrile* (410 mg., 31%), lemon-yellow needles, m. p. 144—145° (Found: C, 54·1; H, 3·3; N, 15·8. $C_8H_6O_3N_2$ requires C, 53·9; H, 3·4; N, 15·7%). Recrystallisation of (iii) from benzene, in which it was only sparingly soluble, furnished *5-hydroxy-2-nitro*-p-*tolunitrile* (250 mg., 19%), pale yellow needles, m. p. 210—211° (decomp.) (Found: C, 54·0; H, 3·3; N, 15·4%). The 5-hydroxy-compound was readily soluble in ethanol and darkened appreciably on prolonged exposure to daylight. The yields (%) of the 3- and 5-hydroxy-compounds were unaltered in an experiment with 6 g. of 3-hydroxy-*p*-tolunitrile.

3-Hydroxy-2-nitro-p-*toluic Acid.*—(a) *By demethylation of* 3-*methoxy-2-nitro*-p-*toluic acid.* 3-Methoxy-2-nitro-*p*-toluic acid (0·1 g.; m. p. 172—173°) (Simonsen and Rau, *loc. cit.*, give m. p. 165—166°) and hydrobromic acid (*d* 1·25; 4 ml.) were heated under reflux for 40 min.

* Part III, preceding paper.

† Toluic acids are now numbered with CO_2H = 1 (see *J.*, 1952, 5088, footnote 13).

Crystallisation of the product from water and finally from benzene furnished **3-*hydroxy*-2-*nitro*-p-*toluic acid***, lemon-yellow plates (56 mg.), m. p. 186—188° (Found: C, 48·6; H, 3·3; N, 7·0. $C_8H_7O_5N$ requires C, 48·7; H, 3·6; N, 7·1%).

(b) *By hydrolysis of* **3-*hydroxy*-2-*nitro*-p-*tolunitrile***. The nitrile (0·2 g.) was heated under reflux for 2 hr. with 2N-sodium hydroxide (5 ml.), and the dark solution acidified (Congo-red) and extracted with ether. Sublimation of the pitch-like extract at 120—130°/10^{-1} mm. yielded a lemon-yellow solid (0·14 g.; m. p. 164—170°) which crystallised from benzene in plates, m. p. 182—184° undepressed by the acid obtained as in (a).

*5-Hydroxy-2-nitro-*p*-toluic Acid.*—5-Hydroxy-2-nitro-*p*-tolunitrile (450 mg.) was heated under reflux for 10 hr. with 2N-sodium hydroxide (10 ml.). Acidification yielded a clear solution which furnished the crude *acid* as a brown solid (360 mg.; m. p. 150—170°) on ether-extraction and recovery. A portion (200 mg.) was sublimed at 130—140°/10^{-1} mm. and crystallised from toluene (50 ml.), forming yellow prisms (160 mg.), m. p. 182° depressed to 150° by the 3-hydroxy-isomer (Found: C, 48·8; H, 3·7; N, 7·1. $C_8H_7O_5N$ requires C, 48·7; H, 3·6; N, 7·1%). It was readily soluble in water, ethanol, acetic acid, acetone and ethyl acetate, but sparingly soluble in benzene.

Hydrolysis of the nitrile for 2 hr. gave mainly the corresponding *amide*, prisms, m. p. 221° (decomp.), from ether (Found: C, 49·1; H, 4·3. $C_8H_8O_4N_2$ requires C, 49·0; H, 4·1%).

Methylation of the toluic acid with methyl sulphate and alkali in the usual way and sublimation of the product at 145°/10^{-1} mm. followed by crystallisation from benzene gave the *methyl ether*, colourless prisms or needles, m. p. 172° depressed to 145° on admixture with the 3-hydroxy-isomer (Found: C, 50·85; H, 4·4; N, 6·7. $C_9H_9O_5N$ requires C, 51·2; H, 4·3; N, 6·6%).

*2-Amino-5-methoxy-*p*-toluic Acid.*—5-Methoxy-2-nitro-*p*-toluic acid (0·2 g.) in ethanol (10 ml.) was hydrogenated at 20° in the presence of a Raney nickel catalyst. Reduction ceased after the uptake of 3 mols. and after removal of the catalyst the product was recovered by evaporation. Sublimation at 130°/10^{-2} mm. and crystallisation from ethanol gave colourless prisms (130 mg.), m. p. 202° (decomp.) with darkening above 195°, of **2-*amino*-5-*methoxy*-p-*toluic acid*** (Found: C, 59·6; H, 5·9. $C_9H_{11}O_3N$ requires C, 59·7; H, 6·1%). It dissolved in 2N-hydrochloric acid, and an ethanol solution showed a violet fluorescence. It gave a transient green colour with ferric chloride in ethanol, changing on dilution with water to deep bluish-purple which soon faded to red-brown. The *acetate*, obtained by 1 hour's heating under reflux with acetic anhydride, crystallised from ethanol in colourless prisms, m. p. 208° (Found: C, 59·1; H, 6·0. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·9%).

2-Amino-5-methoxy-4-methylbenzyl Alcohol.—The above aminotoluic acid (50 mg.) in ether (10 ml.) was added dropwise during 10 min. to lithium aluminium hydride (0·2 g.) in ether (10 ml.). After 3 hours' heating under reflux, excess of hydride was destroyed by water, and then 10% sodium hydroxide (25 ml.) was added. Extraction of the aqueous alkaline layer with ether (3 × 10 ml.) and recovery furnished a gum, purified by sublimation at 90°/10^{-1} mm. and crystallisation from light petroleum (b. p. 60—80°). The **2-*amino*-5-*methoxy*-4-*methylbenzyl alcohol*** (40 mg.) formed colourless needles, m. p. 112° (Found: C, 64·6; H, 7·6; N, 8·2. $C_9H_{13}O_2N$ requires C, 64·65; H, 7·8; N, 8·4%). It gave a green colour with ferric chloride in ethanol.

5-Methoxy-6-methylphthalide.—2-Amino-5-methoxy-4-methylbenzyl alcohol (40 mg.) in hydrochloric acid (0·5 ml.; *d* 1·18) and water (0·5 ml.) was diazotised at 0° with sodium nitrite (30 mg.) in water (0·5 ml.). The cold diazo-solution was added with stirring to a solution of potassium cyanide (0·16 g.) and cupric sulphate (0·14 g.) in water (2 ml.) at 80°, heated for 30 min. at 100°, cooled, and extracted with ether. The red-brown oil obtained on recovery was heated under reflux with 2N-sodium hydroxide (1 ml.) for 7 hr. Acidification (Congo-red), ether-extraction, and recovery yielded a gum, purified by sublimation at 100°/10^{-1} mm. The sublimate (6·5 mg.) crystallised from water in needles, m. p. 144°, of **5-*methoxy*-6-*methylphthalide*** (Found: C, 67·7; H, 6·0. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%). The m. p. was depressed to 115—120° on admixture with 6-methoxy-5-methylphthalide, m. p. 143—145°. The infra-red spectrum was identical with that of the methoxy-methyl-phthalide obtained by methylation of the decarboxylation product of nor*iso*gladiolic acid (Duncanson, Grove, and Zealley, *loc. cit.*). A mixed m. p. determination with the two specimens showed no depression.

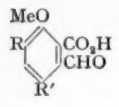
IMPERIAL CHEMICAL INDUSTRIES LIMITED, BUTTERWICK RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS. [*Received, July 28th*, 1953.]

735. *Phthalaldehydes and Related Compounds. Part III.* Synthesis of Deoxygladiolic Acid and Experiments relating to the Structure of Dihydrogladiolic Acid.*

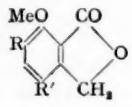
By J. J. Brown and G. T. Newbold.

Treatment of 4-hydroxymethyl-7-methoxy-6-methylphthalide with *N*-bromosuccinimide, followed by hydrolysis of the intermediate bromo-compound, gave deoxygladiolic acid (4-formyl-7-methoxy-6-methylphthalide). The preparation of 3-hydroxymethylopianic acid † from 3-formylopianic acid by catalytic hydrogenation of its monoacetate and subsequent hydrolysis is described. Comparison of the properties of 3-hydroxymethylopianic acid with those of dihydrogladiolic acid shows that the structure of the latter is 3-hydroxymethyl-6-methoxy-5-methylphthalaldehydic acid † rather than 2-hydroxymethyl-3-formyl-6-methoxy-5-methylbenzoic acid as proposed by Raistrick and Ross (*Biochem. J.*, 1952, 635).

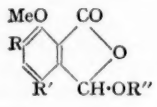
The elegant analytical work of Grove (*Biochem. J.*, 1952, 648) and Raistrick and Ross (*ibid*, p. 635) has established the structure of gladiolic acid, an antifungal metabolic product of *Penicillium gladioli* Machacek, as (I; R = Me, R′ = CHO) tautomeric with (III; R = Me, R′ = CHO, R″ = H) (see Grove, *J.*, 1952, 3345). We have put forward evidence (*J.*, 1952, 4878) in support by an examination of 3-formylopianic acid (I; R = OMe, R′ = CHO), obtained by treatment of 4-chloromethylmeconin (II; R = OMe, R′ = CH_2Cl) with *N*-bromosuccinimide and subsequent hydrolysis. Further synthetical progress was made by the preparation of *iso*gladiolic acid (II; R = Me, R′ = CO_2H) (Brown and Newbold, *J.*, 1953, 1285), the product of alkaline rearrangement of gladiolic acid (Grove, Raistrick, and Ross, *loc. cit.*), by permanganate oxidation of 4-hydroxymethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2·OH).



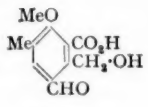
(I)



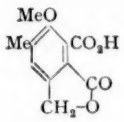
(II)



(III)



(IV)



(V)

The first part of this paper reports the synthesis of deoxygladiolic acid (II; R = Me, R′ = CHO). Our starting material was 4-chloromethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2Cl). Reaction of this compound with three mols. of *N*-bromosuccinimide and hydrolysis of the intermediate bromo-compound gave 4-formyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CHO), identical with deoxygladiolic acid obtained by Grove (*Biochem. J.*, 1952, 648) by reduction of gladiolic acid with iron powder and acetic acid. From the crystallisation mother-liquor of the phthalide there was obtained a trace of crude material which gave a positive ammonia test—a sensitive reaction for gladiolic acid (*loc. cit.*)—but no modification of the reaction conditions gave an isolatable quantity of this compound. Reaction of 4-hydroxymethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2·OH) with three mols. of *N*-bromosuccinimide, followed by hydrolysis, gave 7-methoxy-6-methylphthalide-4-carboxylic acid (II; R = Me, R′ = CO_2H) (*iso*-gladiolic acid); by use of one mol. of reagent deoxygladiolic acid (II; R = Me, R′ = CHO) was obtained in good yield. In the dimethoxy-series 4-hydroxymethylmeconin (II; R = OMe, R′ = CH_2·OH) gave 4-formylmeconin (II; R = OMe, R′ = CHO) with one mol. of *N*-bromosuccinimide, and meconin-4-carboxylic acid (II; R = OMe, R′ = CO_2H) with three mols. 4-Formylmeconin was also obtained by chromic acid oxidation of

* Part II, *J.*, 1953, 1285.

† These structures (I; R = OMe or Me, R′ = CH_2·OH), tautomeric with the lactol forms (III; R = OMe or Me, R′ = CH_2·OH, R″ = H), are used in this paper since we present no evidence which enables a decision to be made between them (see Duncanson, Grove, and Zealley, *J.*, 1953, 3637).

4-hydroxymethylmeconin. We have shown (*J.*, 1952, 4878) that 4-chloromethylmeconin on treatment with three mols. of *N*-bromosuccinimide gave 3-formylopianic acid (I; R = OMe, R′ = CHO) in good yield in contrast to the behaviour of 4-chloromethyl-7-methoxy-6-methylphthalide above. Clearly the methylene group in the phthalide ring in the latter compound is less reactive than that in 4-chloromethylmeconin. *N*-Bromosuccinimide is an electrophilic reagent and attack by it on the 3-methylene group will be facilitated by the presence of an electron-releasing group *para* to it, *i.e.*, in the 6-position. Since the methoxyl group is much more electron-releasing than the methyl group the lack of reactivity of the 3-methylene group in (II; R = Me, R′ = CH_2Cl) to attack by *N*-bromosuccinimide follows.

A further problem in the chemistry of the antifungal metabolic products of *Penicillium gladioli* Machacek was the structure of dihydrogladiolic acid which occurs with gladiolic acid (Raistrick and Ross, *loc. cit.*; Grove, *Biochem. J.*, 1952, 648). Dihydrogladiolic acid has been formulated as (IV) by Raistrick and Ross; such a structure appeared to us unlikely in view of the known instability of *o*-hydroxymethylbenzoic acids, which cyclise when their salts are acidified to give phthalides. Since Raistrick and Ross showed that periodate oxidation of dihydrogladiolic acid gave gladiolic acid in good yield the only other possible structure for the former compound, which must be gladiolic acid with one of the formyl groups reduced to hydroxymethyl, is (I; R = Me, R′ = CH_2·OH). Gladiolic acid not being available to us in quantity we decided to convert 3-formylopianic acid (I; R = OMe, R′ = CHO) into 3-hydroxymethylopianic acid (I; R = OMe, R′ = CH_2·OH) and compare the properties of the latter with those of dihydrogladiolic acid. While this work was being carried out we were informed by Mr. J. F. Grove that his group (Duncanson, Grove, and Zealley, *loc. cit.*) had synthesised the oxidation product of dihydrogladiolic acid described by Raistrick and Ross (*loc. cit.*) and had shown its structure to be (V), thus proving that dihydrogladiolic acid is (I; R = Me, R′ = CH_2·OH).

Treatment of 3-formylopianic acid with acetic anhydride–acetic acid as described by Grove (*loc. cit.*) for the formation of monoacetylgladiolic acid (III; R = Me, R′ = CHO, R″ = Ac) gave the analogous 3-acetoxy-4-formylmeconin (III; R = OMe, R′ = CHO, R″ = Ac), a neutral compound readily hydrolysed to 3-formylopianic acid by boiling dilute sulphuric acid. As in the case of gladiolic acid the action of acetic anhydride in the presence of mineral acid on 3-formylopianic acid gave a triacetate, 3-acetoxy-4-diacetoxymethylmeconin [III; R = OMe, R′ = $CH(OAc)_2$, R″ = Ac]. Hydrogenation of 3-acetoxy-4-formylmeconin in acetic acid in presence of platinum gave, in excellent yield, 3-acetoxy-4-hydroxymethylmeconin (III; R = OMe, R′ = CH_2·OH, R″ = Ac) which was characterized by the formation of its acetate (III; R = OMe, R′ = CH_2·OAc, R″ = Ac). Hydrolysis of the monoacetate (III; R = OMe, R′ = CH_2·OH, R″ = Ac) with dilute alkali at room temperature gave after acidification 3-hydroxymethylopianic acid (I; R = OMe, R′ = CH_2·OH). A similar series of changes were developed independently by Duncanson, Grove, and Zealley (*loc. cit.*) for the conversion of gladiolic acid into dihydrogladiolic acid. In common with dihydrogladiolic acid (Raistrick and Ross, *loc. cit.*) the compound (I; R = OMe, R′ = CH_2·OH) dissolved in sodium hydrogen carbonate solution with effervescence, titrated sharply as a monocarboxylic acid with sodium hydroxide, formed a 2 : 4-dinitrophenylhydrazone, and did not reduce Schiff's reagent, Fehling's solution, or ammoniacal silver nitrate. Oxidation of 3-hydroxymethylopianic acid with sodium metaperiodate in dilute sulphuric acid gave 3-formylopianic acid (I; R = OMe, R′ = CHO) in good yield. On acetylation the compound (I; R = OMe, R′ = CH_2·OH) gave 3-acetoxy-4-acetoxymethylmeconin (III; R = OMe, R′ = CH_2·OAc, R″ = Ac), *i.e.*, the diacetate of the lactol form (III; R = Me, R′ = CH_2·OH, R″ = H). On sublimation 3-hydroxymethylopianic acid gave 4-formylmeconin (II; R = OMe, R′ = CHO) in very low yield [compare the similar formation of deoxygladiolic acid (II; R = Me, R′ = CHO), " dihydrogladiolide," by Raistrick and Ross (*loc. cit.*)]. Raistrick and Ross also describe the formation of deoxygladiolic acid from the acetylation product of dihydrogladiolic acid by boiling mineral acid; this acetylation product described as " dihydrogladiolide diacetate," *i.e.*, [II; R = Me, R′ = $CH(OAc)_2$], must be (III; R = Me, R′ = CH_2·OAc, R″ = Ac) by analogy with the acetylation of 3-hydroxymethylopianic acid described above.

Though 3-formylmeconin was obtained by heating 3-hydroxymethylopianic acid with mineral acid the yield was very poor, much tar being formed, in contrast to the conversion of Raistrick and Ross's diacetate into deoxygladiolic acid. It is therefore evident that a molecular rearrangement takes place during the formation of the latter compound from dihydrogladiolic acid and during the analogous change in the dimethoxy-series.

Reduction by sodium borohydride is a simple method of preparing 4-hydroxymethylphthalides from the vicinal *o*-carboxyphthalaldehydes and derivatives. When 3-formylopianic acid (I; R = OMe, R′ = CHO) was dissolved in aqueous sodium hydrogen carbonate and treated with the reagent at room temperature, 4-hydroxymethylmeconin (II; R = OMe, R′ = CH_2·OH) was obtained in good yield. The same product was also readily formed from 3-acetoxy-4-formylmeconin (III; R = OMe, R′ = CHO, R″ = Ac), 3-acetoxy-4-hydroxymethylmeconin (III; R = OMe, R′ = CH_2·OH, R″ = Ac), and 3-hydroxymethylopianic acid (I; R = OMe, R′ = CH_2·OH) by the action of the same reagent, which with gladiolic acid (I; R = Me, R′ = CHO) gave 4-hydroxymethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2·OH), identical with the synthetic material of Brown and Newbold (*J.*, 1953, 1285).

Since ultra-violet absorption data are available for a number of corresponding compounds in the dimethoxy- and the methylmethoxy-series a comparison has been made in the Table, the position of the maximum nearest to the visible region being given for each compound. In each of the first twelve structures in the Table replacement of the methyl substituent by methoxyl causes a bathochromic shift in the position of maximal absorption in ethanol solution of 16 ± 3 mμ, supporting the chemical evidence of structural similarity between compounds of the two series. The position of maximal absorption in ethanol for dihydrogladiolic acid, in contrast with that for 3-hydroxymethylopianic acid, is dependent on concentration (Duncanson, Grove, and Zealley, *loc. cit.*), showing a large hypsochromic shift with dilution. Chloroform is a better solvent for the comparison of spectral absorption of the two compounds; values for 4-hydroxymethylmeconin (II; R = OMe, R′ = CH_2·OH) and 4-hydroxymethyl-7-methoxy-6-methylphthalide (II; R = Me, R′ = CH_2·OH) in this solvent are included in the Table to indicate that the change of solvent causes no fundamental change in absorption maximum for normal compounds.

(Solvent : ethanol unless otherwise indicated.)

Compound	$\lambda_{max.}$ (mμ) (R = OMe)	$\lambda_{max.}$ (mμ) (R = Me)	Δλ (mμ)
(I; R′ = CHO)	320 [a]	305 [c]	15
(II; R′ = H)	308 [a]	295 [b]	13
(II; R′ = CH_2Cl)	315 [a]	298 [b]	17
(II; R′ = CH_2·OH)	312 [a]	298 [b]	14
	310 [e] ($CHCl_3$)	299 [e] ($CHCl_3$)	11
(II; R′ = CH_2·OAc)	314 [d]	296 [c]	18
(II; R′ = CHO)	324 [c]	306 [c]	18
(II; R′ = CO_2H)	316 [a]	298 [c]	18
(III; R′ = CHO, R″ = Et)	323 [c]	305 [c]	18
(III; R′ = CHO, R″ = Ac)	320 [c]	306 [c]	14
[III; R′ = CH(OAc)$_2$, R″ = Ac]	312 [c]	297 [c]	15
(III; R′ = CH_2·OH, R″ = Ac)	314 [c]	299 [f]	15
(III; R′ = CH_2·OAc, R″ = Ac)	312 [c]	298 [f]	14
(I; R′ = CH_2·OH)	310 [c] (3.7×10^{-4}M)	296 [f] (4.9×10^{-3}M)	14
	308 [c] (3.4×10^{-5}M)	276 [f] (2.2×10^{-4}M)	
	311 [c] ($CHCl_3$)	299 [g] ($CHCl_3$)	12

[a] Brown and Newbold, *J.*, 1952, 4878. [b] *Idem*, *J.*, 1953, 1285. [c] Grove, *J.*, 1952, 3345. [d] This compound was prepared by Brown and Newbold (*J.*, 1952, 4878); it has light absorption in ethanol: Max. at 213 (ε = 28,200) and 314 mμ (ε = 4300). [e] This paper. [f] Grove (personal communication), $\varepsilon_{max.}$ values for (III; R = Me, R′ = CH_2·OH, R″ = Ac), 2500; for (III; R = Me, R′ = CH_2·OAc, R″ = Ac), 3000; and for (I; R = Me, R′ = CH_2·OH, 2050. [g] Duncanson, Grove, and Zealley, *loc. cit.*

Experimental

Ultra-violet absorption spectra were determined in ethanol solution unless otherwise stated. Brominations using *N*-bromosuccinimide were carried out with irradiation from a 60-w lamp adjacent to the flask.

4-Formylmeconin.—(*a*) A solution of 4-hydroxymethylmeconin (500 mg.) (Brown and New-

bold, *J.*, 1952, 4878) in dry carbon tetrachloride (25 c.c.) and dry benzene (25 c.c.) was refluxed with *N*-bromosuccinimide (430 mg., 1 mol.) for 15 min. The filtered mixture was evaporated under reduced pressure and the residual oil heated on the steam-bath with water (50 c.c.) for 1 hr. The cooled mixture was extracted with chloroform (50 c.c.), and the extract washed with sodium hydrogen carbonatesolution (2 × 25 c.c.) and water (2 × 25 c.c.), and dried (Na_2SO_4). Removal of the chloroform under reduced pressure gave a solid which crystallised from methanol, to give 4-*formylmeconin* (170 mg.) as blades, m. p. 195—196° (Found: C, 59·5; H, 4·8. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%). The compound sublimed at 150°/10^{-3} mm. and showed light absorption: Max. at 227 (ε = 20,000), 277 (ε = 4600), 324 (ε = 6000), and inflexion at 240 mμ (ε = 16,000). The 2 : 4-*dinitrophenylhydrazone*, prepared by the action of methanolic 2 : 4-dinitrophenylhydrazine sulphate and washed with methanol, formed needles gradually decomposing but not melting below 350° (Found: N, 13·5. $C_{17}H_{14}O_8N_4$ requires N, 13·9%).

(*b*) 4-Hydroxymethylmeconin (500 mg.), dissolved in glacial acetic acid (10 c.c.), was treated at 15° with chromic anhydride (500 mg.) in glacial acetic acid (10 c.c.) added during 2 min. with stirring. After 5 min. the solution was diluted with water (20 c.c.) and extracted with chloroform (3 × 15 c.c.). The combined chloroform extracts were washed with water (15 c.c.), followed by aqueous sodium hydrogen carbonate (3 × 15 c.c.; 10%) and water (15 c.c.), and dried (Na_2SO_4). Removal of the chloroform gave 4-formylmeconin (300 mg.), separating from methanol as blades, m. p. 196° (Found: C, 60·0; H, 4·2%).

4-*Formyl*-7-*methoxy*-6-*methylphthalide*.—(i) A solution of pure 4-chloromethyl-7-methoxy-6-methylphthalide (284 mg.) (*idem*, *J.*, 1953, 1285) in dry carbon tetrachloride (25 c.c.) was heated under reflux with *N*-bromosuccinimide (670 mg., 3 mols.) for 1½ hr. The filtered mixture was evaporated under reduced pressure, to give a yellow oil which was heated with water (25 c.c.) on the steam-bath for 1 hr. The hot solution was decanted from a little tar and on cooling deposited a solid which on crystallisation from methanol gave 4-*formyl*-7-*methoxy*-6-*methylphthalide* (80 mg.) as needles, m. p. 173—174° alone or mixed with a specimen of deoxygladiolic acid (Found: C, 64·0; H, 5·1. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). Light absorption: Max. at 224 (ε = 23,300), 268 (ε = 8500), and 306 mμ (ε = 4550). The compound sublimed at 120°/10^{-3} mm.

(ii) 4-Hydroxymethyl-7-methoxy-6-methylphthalide (500 mg.) (*loc. cit.*), dissolved in a mixture of benzene and carbon tetrachloride (50 c.c.; 1 : 1), was heated under reflux with *N*-bromosuccinimide (430 mg., 1 mol.) for 15 min. The filtered mixture was evaporated under reduced pressure and the residual solid heated with water (50 c.c.) on the steam-bath for ½ hr., cooled, and extracted with chloroform (3 × 25 c.c.). The combined extracts were washed with water (25 c.c.), aqueous sodium hydrogen carbonate (25 c.c.; 10%), and water (25 c.c.), and dried (Na_2SO_4). Removal of the chloroform and crystallisation of the solid from benzene–light petroleum (b. p. 60—80°) gave 4-formyl-7-methoxy-6-methylphthalide (350 mg.) as needles, m. p. 172—173°, undepressed on mixing with preparation (i) (Found: C, 64·45; H, 5·0%).

Meconin-4-*carboxylic Acid*.—4-Hydroxymethylmeconin (500 mg.) was refluxed with *N*-bromosuccinimide (1·2 g., 3 mols.) in carbon tetrachloride (25 c.c.) and benzene (25 c.c.) for 20 min. The reaction mixture was hydrolysed and worked up as in (ii), to give a neutral fraction from which 4-formylmeconin (20 mg.) was obtained, separating from methanol as blades, m. p. 193° undepressed by the preparation above. The acidic fraction crystallised from aqueous ethanol (charcoal), to give meconin-4-carboxylic acid (150 mg.) as needles, m. p. and mixed m. p. 220—221° (*idem*, *J.*, 1952, 4878) (Found: C, 55·7; H, 4·4. Calc. for $C_{11}H_{10}O_6$: C, 55·5; H, 4·2%). Light absorption: Max. at 216 (ε = 28,700) and 318 mμ (ε = 6000).

7-*Methoxy*-6-*methylphthalide*-4-*carboxylic Acid*.—4-Hydroxymethyl-7-methoxy-6-methylphthalide (250 mg.) was treated with *N*-bromosuccinimide (3 mols.) as in the foregoing experiment. No crystalline material was obtained from the neutral fraction. The acidic fraction gave 7-methoxy-6-methylphthalide-4-carboxylic acid (150 mg.), separating from aqueous ethanol as needles, m. p. 232—233° alone or mixed with *iso*gladiolic acid (Found: C, 59·5; H, 4·8. Calc. for $C_{11}H_{10}O_5$: C, 59·5; H, 4·5%). Light absorption: Max. at 216 (ε = 34,000), 298 (ε = 4800), and inflexion at 248 mμ (ε = 8,500).

3-*Acetoxy*-4-*formylmeconin*.—3-Formylopianic acid (500 mg.) (*loc. cit.*) was heated with acetic anhydride (5 c.c.) and glacial acetic acid (5 c.c.) on the steam-bath for 1½ hr. The cooled solution was poured on ice (30 g.), and the mixture extracted with chloroform (3 × 30 c.c.). The chloroform extract was washed with water, sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). Removal of the chloroform under reduced pressure followed by crystallisation from ethanol gave 3-*acetoxy*-4-*formylmeconin* (400 mg.) as needles, m. p. 177° (Found:

C, 55·7; H, 4·5. $C_{13}H_{12}O_7$ requires C, 55·7; H, 4·3%). Light absorption: Max. at 235 (ε = 18,500), 280 (ε = 3700) and 320 mμ (ε = 4300). It is most important that the reaction mixture should be free from mineral acid since the presence of a trace of the latter causes formation of 3-acetoxy-4-diacetoxymethylmeconin.

3-*Acetoxy*-4-*diacetoxymethylmeconin*.—3-Formylopianic acid (100 mg.), suspended in acetic anhydride (2 c.c.), was treated with sulphuric acid (1 drop; *d* 1·84); dissolution took place rapidly. The solution was heated on the steam-bath for 5 min., cooled, and poured on ice. The precipitate was collected and crystallised from aqueous ethanol from which 3-*acetoxy*-4-*diacetoxymethylmeconin* (120 mg.) separated as needles, m. p. 120—121° (Found: C, 53·5; H, 5·0. $C_{17}H_{18}O_{10}$ requires C, 53·4; H, 4·75%). Light absorption: Max. at 219 (ε = 29,400) and 312 mμ (ε = 4000).

3-*Acetoxy*-4-*hydroxymethylmeconin*.—3-Acetoxy-4-formylmeconin (1·43 g.), partly dissolved in glacial acetic acid (150 c.c.), was added to a suspension of freshly reduced platinum (from Adams platinum oxide; 300 mg.) in glacial acetic acid (25 c.c.), and the mixture shaken with hydrogen at room temperature for 3 hr., by which time absorption (150 c.c.; calc., 135 c.c. for 1 mol.) had ceased. Removal of the catalyst and evaporation under reduced pressure gave an oil which rapidly solidified. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave 3-*acetoxy*-4-*hydroxymethylmeconin* (1·1 g.) as needles, m. p. 136° (Found: C, 55·5; H, 5·2. $C_{13}H_{14}O_7$ requires C, 55·3; H, 5·0%). Light absorption: Max. at 218 (ε = 31,400) and 314 mμ (ε = 4200).

3-*Hydroxymethylopianic Acid*.—3-Acetoxy-4-hydroxymethylmeconin (1·08 g.) was treated with aqueous sodium hydroxide (60 c.c.; 0·1N) at room temperature; dissolution was rapid. After 2 min. the solution was acidified (Congo-red) with hydrochloric acid (*d* 1·16) and stored at 0° overnight. The solid which had separated was collected, washed with water, dried over phosphoric oxide *in vacuo*, and crystallised from ethyl acetate–light petroleum (b. p. 60—80°), to give 3-*hydroxymethylopianic acid* (500 mg.) as fine needles, m. p. 141° (Found: C, 55·2; H, 5·2%; equiv., 235. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%; equiv., 240). Light absorption: Max. at 216 (ε = 27,400) and 308 mμ (ε = 3500) in ethanol; 246 (ε = 3900) and 311 mμ (ε = 3150) in chloroform. The 2 : 4-*dinitrophenylhydrazone* separated from ethanol as red needles, which shrink at 215—220° and decompose gradually as the temperature is raised to 350° (Found: N, 13·5. $C_{17}H_{16}O_9N_4$ requires N, 13·3%). 3-Hydroxymethylopianic acid gave no colour with aqueous ammonia (*d* 0·88), and did not reduce Schiff's reagent, Fehling's solution, or ammoniacal silver nitrate.

4-*Formylmeconin from* 3-*Hydroxymethylopianic Acid*.—(*a*) The acid (140 mg.) was heated under reflux with sulphuric acid (5 c.c.; 2N) for 4½ hr. The red solution was decanted from tar and cooled, and the solid collected, washed with sodium hydrogen carbonate solution, and water, and crystallised from methanol. 4-Formylmeconin (10 mg.) separated as blades, m. p. 194—195° alone or mixed with an authentic specimen (Found: C, 59·4; H, 4·9. Calc. for $C_{11}H_{10}O_5$: C, 59·5; H, 4·5%).

(*b*) 3-Hydroxymethylopianic acid (100 mg.) was heated to 200° and the melt sublimed at 190°/10^{-3} mm. The small amount of sublimate was crystallised from methanol to give 4-formylmeconin (2 mg.) as blades, m. p. 192—193° alone or mixed with preparation (*a*).

3-*Acetoxy*-4-*acetoxymethylmeconin*.—(*a*) 3-Acetoxy-4-hydroxymethylmeconin (40 mg.) in dry pyridine (0·2 c.c.) and acetic anhydride (0·2 c.c.) was kept at room temperature overnight. The product was precipitated by addition of water (5 c.c.), separated, and crystallised from aqueous ethanol from which 3-*acetoxy*-4-*acetoxymethylmeconin* (38 mg.) formed needles, m. p. 124° (Found: C, 55·7; H, 5·3. $C_{15}H_{16}O_8$ requires C, 55·55; H, 5·0%). Light absorption: Max. at 218 (ε = 30,800) and 213 mμ (ε = 4000).

(*b*) 3-Hydroxymethylopianic acid (50 mg.) was acetylated as in (*a*), giving 3-acetoxy-4-acetoxymethylmeconin (50 mg.) which separated from aqueous ethanol as needles, m. p. 125° alone or mixed with preparation (*a*) (Found: C, 55·4; H, 5·3%).

3-*Ethoxy*-4-*formylmeconin*.—A solution of 3-formylopianic acid (500 mg.) in dry ethanol (5 c.c.), with sulphuric acid (5 drops; *d* 1·84) added, was heated under reflux for 30 min. The cooled solution was diluted with water and extracted with ether, and the ethereal extract washed with sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). Removal of the ether and crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave 3-ethoxy-4-formylmeconin (200 mg.) as needles, m. p. 107—108° (Found: C, 58·6; H, 5·5. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%). Light absorption: Max. at 230 (ε = 16,800), 278 (ε = 3700), and 323 mμ (ε = 3900).

4-*Hydroxymethylmeconin*.—(*a*) A solution of 3-formylopianic acid (250 mg.) in sodium hydro-

gen carbonate solution (15 c.c.; 10%) was treated at room temperature with sodium borohydride (250 mg.) and stored overnight. The solution was acidified (Congo-red) with dilute hydrochloric acid and extracted with chloroform (3 × 20 c.c.). The combined extracts were washed with water (20 c.c.), dried (Na_2SO_4), and evaporated. Crystallisation of the residue from benzene gave 4-hydroxymethylmeconin (200 mg.) as needles, m. p. 129° alone or mixed with a specimen prepared by Brown and Newbold (*J.*, 1952, 4878) (Found: C, 59·0; H, 5·7. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%). Light absorption in ethanol: Max. at 212 (ε = 28,600) and 312 mμ (ε = 4100); in chloroform: Max. at 244 (ε = 5750) and 310 mμ (ε = 4400).

(*b*) A solution of 3-acetoxy-4-formylmeconin (150 mg.) in ethanol (30 c.c.) was added to a solution of sodium borohydride (150 mg.) in water (10 c.c.) at room temperature and kept for 5 hr. Working up as in (*a*) gave 4-hydroxymethylmeconin (70 mg.) which separated from benzene as needles, m. p. 127° alone or mixed with preparation (*a*) (Found: C, 59·25; H, 5·55%).

(*c*) A suspension of 3-acetoxy-4-hydroxymethylmeconin (50 mg.) in water (10 c.c.) was shaken with sodium borohydride (250 mg.) with warming to 40°, until dissolution was complete (5 min.). The solution was stored overnight at room temperature and worked up as in (*a*), to give 4-hydroxymethylmeconin (37 mg.), separating from benzene as needles, m. p. 127—128° alone or mixed with preparation (*a*) or (*b*) (Found: C, 58·65; H, 5·5%). 4-Hydroxymethylmeconin was similarly obtained from sodium borohydride reduction of 3-hydroxymethylopianic acid, and had m. p. and mixed m. p. 128°. The *benzoyl* derivative, prepared by the action of benzoyl chloride–pyridine on 4-hydroxymethylmeconin at room temperature overnight followed by working up *via* ether, separated from ethanol as needles, m. p. 131—132° (Found: C, 66·1; H, 5·2. $C_{18}H_{16}O_6$ requires C, 65·85; H, 4·9%).

4-Hydroxymethyl-7-methoxy-6-methylphthalide.—Gladiolic acid (100 mg.), dissolved in sodium hydrogen carbonate solution (10 c.c.; 10%), was treated with sodium borohydride (200 mg.) added in one portion at room temperature, and the solution was stored overnight, then acidified (Congo-red) with 3N-hydrochloric acid and extracted with chloroform (3 × 15 c.c.). The combined chloroform extracts were washed once with water, dried (Na_2SO_4), and evaporated, and the solid crystallised from benzene, to give 4-hydroxymethyl-7-methoxy-6-methylphthalide (80 mg.) as needles, m. p. 119° alone or mixed with a specimen prepared by Brown and Newbold (*J.*, 1953, 1285) (Found: C, 63·8; H, 6·0. Calc. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·8%). Light absorption in ethanol: Max. at 212 (ε = 28,000), 237 (ε = 6200) and 298 mμ (ε = 3000); in chloroform: Max. at 244 (ε = 2250) and 299 mμ (ε = 3200). The *acetate*, prepared by the action of acetic anhydride and pyridine at room temperature overnight, separated from aqueous ethanol as needles, m. p. 95° (Found: C, 62·5; H, 5·8. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). The compound sublimed rapidly at 90°/10^{-3} mm., and showed light absorption: Max. at 212 (ε = 33,800), 296 (ε = 3500), and an inflexion at 234 mμ (ε = 8200).

3-Formylopianic Acid.—3-Hydroxymethylopianic acid (170 mg.) was heated under reflux with a solution of sodium metaperiodate (500 mg.) in N-sulphuric acid (5 c.c.) for 15 min. The cooled solution deposited a crystalline sodium salt. This was dissolved in aqueous sodium carbonate (10%) and acidified (Congo-red) with hydrochloric acid (5N). The precipitated solid was crystallised from water, to give 3-formylopianic acid (105 mg.) as needles, m. p. and mixed m. p. 175—176° (Found: C, 55·6; H, 4·4. Calc. for $C_{11}H_{10}O_6$: C, 55·5; H, 4·2%).

The authors thank Professor F. S. Spring, F.R.S., for his continued encouragement, Mr. J. F. Grove, whose co-operation has been most valuable, the Governors of The Royal Technical College for the award of the Nobel Scholarship (to J. J. B.), and Messrs. T. & H. Smith, Ltd., for gifts of chemicals. The microanalyses were by Mr. Wm. McCorkindale and the ultra-violet absorption spectra were measured by Miss Elizabeth Davidson. Mr. J. McDonald gave some experimental assistance.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, July 15th,* 1953.]

736. *Studies in the Pyrrocoline Series.*

By E. D. Rossiter and J. E. Saxton.

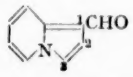
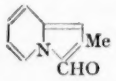
2-Methylpyrrocoline has been formylated to give 3-formyl- or 1 : 3-diformyl-2-methylpyrrocoline. The former was identified by reduction to 2 : 3-dimethylpyrrocoline.

2 : 3-Dimethylpyrrocoline has been formylated to 1-formyl-2 : 3-dimethylpyrrocoline, Wolff–Kishner or lithium aluminium hydride reduction of which gives 1 : 2 : 3-trimethylpyrrocoline. This behaviour is analogous to that of 3-formylindole and 3-acetylindole.

When 2-methylpyrrocoline reacts with methyl iodide the first methyl group enters the 3-, and the second the 1-position.

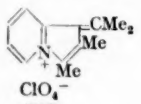
2 : 3-Dimethylpyrrocoline gives a Mannich base with formaldehyde and dimethylamine, the methiodide of which behaves as an alkylating agent in a manner analogous to that of gramine methiodide in the indole series.

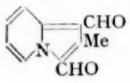
There have hitherto been no reports of the preparation and properties of aldehydes in the pyrrocoline series. While they may be regarded simply as aromatic aldehydes, it is conceivable that their properties may be influenced by the presence of nitrogen in the molecule. For example, 1-formylpyrrocoline (I) may be regarded as the vinylogue of an amide. For the first experiments, the readily available 2-methylpyrrocoline was chosen.

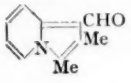
(I)   (II)

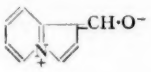
Since the pyrrocoline and the indole ring system frequently show similar reactivity, the 1- and the 3-position of pyrrocoline being analogous to the 2- and the 3-position of indole, it should be possible to formylate 2-methylpyrrocoline with the reagents successful in the indole series. In general, electrophilic reagents attack pyrrocolines in the 3-position, and, if this is substituted, the 1-position. There is one known exception, namely, the nitration of 2-methylpyrrocoline, which gives 2-methyl-1-nitropyrrocoline in addition to the 3-nitro-isomer (Borrows, Holland, and Kenyon, *J.*, 1946, 1077). Hence the structure of any formylation product requires proof. 2-Methylpyrrocoline with *N*-methylformanilide and phosphorus oxychloride gave 3-formyl-2-methylpyrrocoline (II), though the yield was small owing, probably, to the acid medium used in the reaction: the formyl group was quantitatively removed by hot dilute mineral acid in 2 min.

The structure of (II) was proved by Wolff–Kishner reduction to 2 : 3-dimethylpyrrocoline, and preparation of the latter according to Ochiai and Tsuda's method (*Ber.*, 1934, **67**, 1011). The melting point (39·5—40·5°) of our samples of 2 : 3-dimethylpyrrocoline was somewhat higher than that recorded by Ochiai and Tsuda (35—36°). This may be due partially to the use of purer starting material, but is probably mainly due to purification of the product by sublimation, by far the most satisfactory technique for low-melting pyrrocolines.


(III)


(IV)


(V)


(Va)

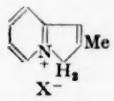
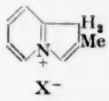
2 : 3-Dimethylpyrrocoline is a weaker base than 2-methylpyrrocoline, and under ordinary conditions does not form a picrate; it was therefore characterised as the perchlorate. Crystallisation of the latter from acetone containing perchloric acid gave a derivative, $C_{13}H_{16}O_4NCl$, which is presumably 2 : 3-dimethyl-1-*iso*propylidenepyrrocolinium perchlorate (III).

Under Reimer–Tiemann conditions 2-methylpyrrocoline gave 1 : 3-diformyl-2-methylpyrrocoline (IV). It was hoped that the formyl group in the more reactive 3-position might be removed preferentially by acid hydrolysis, but this proved to be impracticable.

2 : 3-Dimethylpyrrocoline was formylated to 1-formyl-2 : 3-dimethylpyrrocoline (V), the structure of which was proved by Wolff–Kishner reduction to 1 : 2 : 3-trimethylpyrrocoline and unambiguous synthesis of the latter. Reduction of (V) with lithium aluminium hydride gave mainly 1 : 2 : 3-trimethylpyrrocoline. In this respect it behaves more like an amide than an aldehyde, possibly owing to participation in the structure of canonical forms such as (V*a*). This is reflected in the decreased tendency of both (II) and (V) to yield derivatives of the carbonyl group. Thus 1-formyl-2 : 3-dimethylpyrrocoline reacts only sluggishly with semicarbazide in ethanol, fails to undergo the Cannizzaro reaction (this may, however, be partly due to steric hindrance), and cannot be oxidised by silver oxide. 3-Formyl-2-methylpyrrocoline is even less reactive, and could not even be induced to form a semicarbazone.

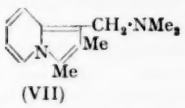
The complete elimination of oxygen on reduction of the carbonyl group with lithium aluminium hydride is found also in the indole series. 3-Formylindole and 3-acetylindole are reduced by an excess of reducing agent to skatole and 3-ethylindole. These carbonyl compounds can again be regarded as vinylogues of amides.

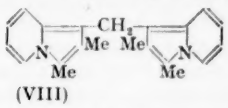
It was pointed out by one of the present authors (*J.*, 1951, 3240) that the pyrrocolinium ion contains a true pyridine ring. Thus 2-methylpyrrocolinium salts can be represented by VI(*a* or *b*), the former being the more probable. Reaction of 2-methylpyrrocoline with

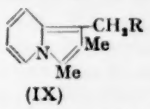
(VI*a*)  (VI*b*) 

methyl iodide at room temperature gave a crystalline product, identified as the hydriodide of 2-methylpyrrocoline. The much weaker basic product of methylation remained in the mother-liquors, and could not be separated from unchanged 2-methylpyrrocoline by fractional crystallisation of base or picrate, by fractional sublimation, or by chromatography. The methylation product was finally identified as 2 : 3-dimethylpyrrocoline by formylation of the mixture of bases obtained from the mother-liquors. 1-Formyl-2 : 3-dimethylpyrrocoline was isolated and identified, thus showing that attack by methyl iodide was first at the 3-position. This favours (VI*a*) as the formula of the ion from 2-methylpyrrocoline. Further methylation with methyl iodide at elevated temperatures gave 1 : 2 : 3-trimethylpyrrocoline and its methiodide.

The analogy between pyrrocolines and indoles has been further demonstrated by preparation of the Mannich base (VII) from 2 : 3-dimethylpyrrocoline. A by-product $C_{21}H_{22}N_2$ is considered to be di-(2 : 3-dimethyl-1-pyrrocolinyl)methane (VIII) and was readily obtainable by the direct condensation of 2 : 3-dimethylpyrrocoline and formaldehyde. The salts of the Mannich base are very unstable, and decompose more readily


(VII)


(VIII)


(IX)

than the corresponding salts of gramine. In consequence the methiodide of (VII) behaves as an alkylating agent : with sodium methoxide it gives 1-methoxymethyl-2 : 3-dimethylpyrrocoline (IX; R = OMe), and with potassium cyanide it readily gives 1-cyanomethyl-2 : 3-dimethylpyrrocoline (IX; R = CN).

1 : 2-Dimethyl- and 2-ethyl-pyrrocoline and their derivatives are also described below.

Experimental

3-Formyl-2-methylpyrrocoline.—*N*-Methylformanilide (15·6 g.) and phosphorus oxychloride (17·8 g.) were mixed, with mechanical stirring and exclusion of atmospheric moisture. After 15 min. at room temperature, ethylene dichloride (75 g.) was added and the solution cooled in an ice-bath. When the internal temperature had reached 0°, 2-methylpyrrocoline (6 g.), dissolved in a small amount of ethylene dichloride, was added dropwise at such a rate that the temperature did not rise above 10°. The mixture was kept at 0° for a further hour with

stirring, finely divided calcium carbonate (20 g.) was added, and the ice-bath removed. The mixture was gently heated, with stirring; a violent reaction occurred, external cooling sometimes being necessary. When the reaction had subsided the mixture was heated under reflux for 2 hr., then cooled and poured into a mixture of sodium acetate (75 g.), water (75 c.c.), and ice (15 g.). The ethylene dichloride and unchanged 2-methylpyrrocoline were removed in steam (500 c.c. of distillate) : continuation of the distillation gave a pale green distillate, from which needles gradually separated. The solid was collected and crystallised from light petroleum (b. p. 40—60°). 3-*Formyl*-2-*methylpyrrocoline* (0·6 g., 8·2%) was obtained as pale green rhombs, m. p. 56·5—57·5° (Found : C, 75·6; H, 5·5; N, 8·6. $C_{10}H_9ON$ requires C, 75·4; H, 5·7; N, 8·8%).

The aldehyde (0·05 g.) was triturated with a few drops of 60% aqueous perchloric acid. Addition of ether gave a yellow precipitate of the *hemi-perchlorate*, m. p. 173—175° (decomp.) after darkening at 140° and sintering at 160° (Found : C, 57·2, 57·7; H, 4·7, 4·5; N, 7·2; Cl, 9·0. $C_{20}H_{19}O_6N_2Cl$ requires C, 57·3; H, 4·5; N, 6·7; Cl, 8·5%). 3-Formyl-2-methylpyrrocoline failed to give a silver mirror or a semicarbazone, but gave a dark red precipitate, decomp. 200°, with 2 : 4-dinitrophenylhydrazine in concentrated sulphuric acid and ethanol. Attempts to purify this derivative by recrystallisation from ethyl acetate were unsuccessful.

The formyl group was quantitatively removed in 2 min. by an excess of boiling 2N-hydrochloric acid.

In the infra-red region the carbonyl band is at 6·10 μ.

Reduction of 3-*Formyl*-2-*methylpyrrocoline*.—3-Formyl-2-methylpyrrocoline (1 g.), 100% hydrazine hydrate (4·3 c.c.), ethanol (40 c.c.), and sodium ethoxide (from 2 g. of sodium) were heated together at 180° for 22 hr. The *azine* which separated was collected at the pump, recrystallised from tetrahydrofuran, and obtained as orange needles, m. p. 254° (decomp.) (1 g., 51%) (Found : C, 76·8, 76·2; H, 6·0, 5·8; N, 17·8. $C_{20}H_{18}N_4$ requires C, 76·4; H, 5·7; N, 17·8%).

The filtrate from the reaction mixture was diluted with water, and the base isolated by means of ether and purified by sublimation at 100°/20 mm. 2 : 3-Dimethylpyrrocoline (0·1 g.) was obtained as colourless plates with a blue fluorescence, m. p. 39·5—40·5°, alone or mixed with authentic 2 : 3-dimethylpyrrocoline (Found : C, 82·9; H, 7·8; *C*-Me, 20·4. Calc. for $C_{10}H_{11}N$: C, 82·8; H, 7·6; 2*C*-Me, 20·8%).

2 : 3-*Dimethylpyrrocoline*.—This was prepared according to Ochiai and Tsuda's method (*Ber.*, 1934, **67**, 1011) from pure 1-bromoethyl methyl ketone and α-picoline, and purified by sublimation at 100°/20 mm. 2 : 3-Dimethylpyrrocoline was obtained as colourless plates with a blue fluorescence, m. p. 39·5—40·5°.

Freshly sublimed 2 : 3-dimethylpyrrocoline (0·05 g.) was triturated with aqueous perchloric acid (0·2 c.c. of 60%), then ether was added to complete the precipitation. The *perchlorate* of 2 : 3-dimethylpyrrocoline was obtained from methanol as colourless rhombs with a slight blue tinge, m. p. 74—75·5° (Found : C, 49·1; H, 5·1. $C_{10}H_{12}O_4NCl$ requires C, 48·9; H, 4·9%). Recrystallisation of this from acetone containing an excess of perchloric acid yielded 2 : 3-*dimethyl*-1-iso*propylidenepyrrocolinium perchlorate*, yellow needles, which darkened above 225°, decomp. 230—233° (Found : C, 54·7; H, 5·5. $C_{13}H_{16}O_4NCl$ requires C, 54·6; H, 5·6%).

1 : 3-*Diformyl*-2-*methylpyrrocoline*.—A boiling solution of 2-methylpyrrocoline (10 g.) in chloroform (85 c.c.) and ethanol (200 c.c.) was stirred, and a solution of potassium hydroxide (125 g.) in water (150 c.c.) added during 2½ hr. ; boiling was continued for a further 30 min. and the mixture then cooled. The potassium chloride which separated was removed by filtration, the solid was washed with chloroform, and the washings were added to the filtrate, which was then distilled in steam. When all the chloroform had been removed the steam-distillation was continued until approx. 500 c.c. of pale green distillate had been collected. This was extracted with ether, the ethereal layer was dried (Na_2SO_4), the ether removed, and the residue recrystallised from light petroleum (b. p. 40—60°). A small amount of 3-formyl-2-methylpyrrocoline was obtained as pale green needles, m. p. and mixed m. p. 56·5—57·5°. The mother-liquors from the steam-distillation were filtered whilst hot, and the residue extracted with boiling water (6 × 500 c.c.) (charcoal). The solid which separated from the combined filtrates was recrystallised from tetrahydrofuran, giving 1 : 3-*diformyl*-2-*methylpyrrocoline* (7 g., 49%) as pale yellow needles, m. p. 210° (Found : C, 70·8; H, 4·8; N, 7·3. $C_{11}H_9O_2N$ requires C, 70·6; H, 4·8; N, 7·5%).

1 : 3-Diformyl-2-methylpyrrocoline failed to give a silver mirror but gave a dark-red precipitate with 2 : 4-dinitrophenylhydrazine in concentrated sulphuric acid and ethanol. The *phenylhydrazone*, prepared in 30% acetic acid, formed golden-yellow plates (from methanol),

m. p. 177—179° (decomp.) (sintering above 170°) (Found: C, 74·0; H, 5·5; N, 14·8. $C_{17}H_{15}ON_3$ requires C, 73·6; H, 5·4; N, 15·2%). Attempts to remove the 3-formyl group selectively by various mixtures of hydrochloric and acetic acids failed.

1-*Formyl*-2 : 3-*dimethylpyrrocoline*.—2 : 3-Dimethylpyrrocoline (6 g.) was formylated with *N*-methylformanilide (15·6 g.) and phosphorus oxychloride (17·8 g.) as described for 2-methylpyrrocoline. After removal of the ethylene dichloride in steam, the mother-liquors were diluted with water (750 c.c.), boiled (charcoal), and filtered. The residue was extracted with boiling water (2 × 500 c.c.). The solid which separated from the cooled filtrates was dried and recrystallised from light petroleum (b. p. 60—80°) (charcoal). 1-*Formyl*-2 : 3-*dimethylpyrrocoline* (2·6 g., 36%) was obtained as colourless needles, m. p. 94—95° (Found: C, 76·3; H, 6·4; N, 7·9. $C_{11}H_{11}ON$ requires C, 76·5; H, 6·3; N, 8·0%). 1-Formyl-2 : 3-dimethylpyrrocoline failed to give a silver mirror, but gave a dark red precipitate with 2 : 4-dinitrophenylhydrazine in concentrated sulphuric acid and ethanol. In the infra-red region the carbonyl bands are at 6·08 and 6·17 μ.

The *semicarbazone*, prepared in anhydrous ethanol, was obtained from tetrahydrofuran as yellow-green prisms, m. p. 209° (Found: C, 63·2, 63·5; H, 6·8, 6·7; N, 21·4, 21·4. $C_{12}H_{14}ON_4,\frac{1}{2}C_4H_8O$ requires C, 63·2; H, 6·8; N, 21·1%) (Found, on sample dried at 100° for 4 hr.: C, 61·9; H, 6·0; N, 25·3. $C_{12}H_{14}ON_4$ requires C, 62·6; H, 6·1; N, 24·4%). The *perchlorate* crystallised from water as pale yellow needles, decomp. 194—196° (sinters at 155°, becomes green at 185°) (Found: C, 45·1; H, 4·7. $C_{11}H_{14}O_6NCl$ requires C, 45·6; H, 4·8%).

Reduction of 1-*Formyl*-2 : 3-*dimethylpyrrocoline*.—1-Formyl-2 : 3-dimethylpyrrocoline (1 g.), 100% hydrazine hydrate (4·3 c.c.), and metallic sodium (2 g.), dissolved in ethanol (40 c.c.), were heated together at 200° for 24 hr. The resulting solution was filtered, diluted with water, and extracted with ether. The semi-solid amber product obtained on removal of the ether was sublimed at 100°/20 mm. on to a cold finger cooled with solid carbon dioxide and ethanol. 1 : 2 : 3-*Trimethylpyrrocoline* was obtained as colourless plates, m. p. 12—13° (Found: N, 8·8. $C_{11}H_{13}N$ requires N, 8·8%). The *perchlorate* formed colourless prisms, m. p. 126—128°, from methanol (Found: C, 50·8; H, 5·6; N, 5·4; Cl, 13·8. $C_{11}H_{14}O_4NCl$ requires C, 50·9; H, 5·4; N, 5·4; Cl, 13·7%).

Reduction of 1-*Formyl*-2 : 3-*dimethylpyrrocoline with Lithium Aluminium Hydride*.—1-Formyl-2 : 3-dimethylpyrrocoline (1 g.) in dry ether (100 c.c.) was added dropwise to a stirred solution of lithium aluminium hydride (1 g.) in dry ether (100 c.c.). The mixture was then heated under reflux for 2 hr. and set aside for a further 36 hr. Dilute sulphuric acid (100 c.c.) was added, the ethereal layer was dried, and the solvent removed. The residual oil (0·5 g.) was distilled, and collected at 55°/0·07 mm. (bath-temp.). The crude 1 : 2 : 3-trimethylpyrrocoline so obtained was purified by sublimation at 100°/20 mm. on to a cold finger, and obtained as colourless plates with a blue fluorescence, m. p. 12—13°. The perchlorate formed colourless prisms, m. p. and mixed m. p. 126—128°, from methanol (Found: C, 50·9; H, 5·7; N, 5·3; Cl, 13·8%).

1 : 2 : 3-*Trimethylpyrrocoline*.—A mixture of 2-ethylpyridine (10 g.) and 1-bromoethyl methyl ketone (15·5 g.) was heated on a steam-bath for 3 hr. and allowed to cool. The resulting brown solid was washed with ethanol–ether (1 : 1; 20 c.c.) and dissolved in distilled water (400 c.c.). Sodium hydrogen carbonate (25 g.) was added to the solution, which was heated on a steam-bath for 1 hr. and then distilled in steam. The pale yellow oil which separated from the aqueous distillate was extracted with ether, and the ethereal layer was dried and distilled. 1 : 2 : 3-Trimethylpyrrocoline (10 g., 67%), b. p. 85—87°/0·095 mm., was obtained as a pale yellow oil, rapidly darkening in air and light (Found: C, 82·9; H, 8·0; N, 9·2. Calc. for $C_{11}H_{13}N$: C, 83·0; H, 8·2; N, 8·8%). The perchlorate formed prisms, m. p. and mixed m. p. 126—128°. The *picrate* was obtained from ethanol as a yellow microcrystalline solid, m. p. 94—95° (decomp.) (Found: C, 52·8; H, 4·2. $C_{17}H_{16}O_7N_4$ requires C, 53·1; H, 4·1%).

Reduction of 3-*Formylindole*.—3-Formylindole (0·19 g.) in pure tetrahydrofuran (25 c.c.) was added dropwise during 90 min. to lithium aluminium hydride (0·2 g.) in ether (80 c.c.). The solution was heated under reflux for 2 hr., then cooled, and the excess of reagent destroyed by addition of ethanol and dilute hydrochloric acid. The organic layer was dried and evaporated. The residue crystallised from light petroleum (b. p. 40—60°) as colourless plates, m. p. 92—94°, having a pronounced skatole odour. The picrate was prepared in benzene, and obtained as red needles, m. p. and mixed m. p. with skatole picrate, 171—172°.

Reduction of 3-*Acetylindole*.—This was reduced with excess of lithium aluminium hydride as described above for 3-formylindole. The product was converted into its picrate, which was obtained from benzene as red needles, m. p. and mixed m. p. with authentic 3-ethylindole

picrate, 120—121° (Found : C, 51·7; H, 3·9; N, 14·7. Calc. for $C_{10}H_{11}N,C_6H_3O_7N_3$: C, 51·35; H, 3·75; N, 15·0%).

Reaction of 2-Methylpyrrocoline with Methyl Iodide.—(a) *2-Methylpyrrocoline hydriodide.* A solution of freshly sublimed 2-methylpyrrocoline (6 g.) in methyl iodide (20 c.c.) was set aside overnight. Ether was then added to complete the precipitation of the salt, which was collected, washed with ether, and recrystallised from ethanol. *2-Methylpyrrocoline hydriodide* (5·5 g., 42%) was obtained as colourless rhombs, m. p. 165—170° (decomp.), which in air and light became dark green (Found : C, 41·9; H, 4·1; I, 48·9. $C_9H_{10}NI$ requires C, 41·7; H, 3·9; I, 49·0%).

(b) *Identification of 2 : 3-dimethylpyrrocoline.* A solution of freshly sublimed 2-methylpyrrocoline (4·3 g., 2 mols.) and methyl iodide (2·85 g., 1 mol.) in methanol (30 c.c.) was heated at 100° for 3 hr. The solvent was then removed, the crude 2-methylpyrrocoline hydriodide was washed well with dry ether, and the combined ethereal washings were dried and evaporated. The mixture of 2-methylpyrrocoline and 2 : 3-dimethylpyrrocoline was sublimed at 100°/20 mm. This mixture (1·5 g.) was then formylated as described above for pure 2 : 3-dimethylpyrrocoline, the 3-formyl-2-methylpyrrocoline being removed in the steam-distillation. 1-Formyl-2 : 3-dimethylpyrrocoline (0·1 g.) was obtained from light petroleum (b. p. 60—80°) as colourless needles, m. p. and mixed m. p. 93—94°, identity being confirmed by comparison of infra-red spectra.

(c) *1 : 2 : 3-Trimethylpyrrocoline methiodide.* 2-Methylpyrrocoline (7 g.), methyl iodide (25 c.c.), and methanol (30 c.c.) were heated together at 100° for 24 hr. The solvent was removed and the residue triturated with acetone until crystallisation was complete. The solid was collected, washed with acetone, and recrystallised from the same solvent. *1 : 2 : 3-Trimethylpyrrocoline methiodide* (4 g.) was obtained as pale brown rhombs, m. p. 197·5° (sinters above 180°) (Found : C, 47·9; H, 5·6; I, 42·3. $C_{12}H_{16}NI$ requires C, 47·8; H, 5·3; I, 42·2%). A solution of the pure methiodide in water gave no precipitate on basification with sodium hydroxide solution.

(d) *1 : 2 : 3-Trimethylpyrrocoline.* 2-Methylpyrrocoline (2·1 g.), methyl iodide (10 c.c.), and methanol (10 c.c.) were heated together at 100° for 24 hr. The solvent was then removed, the crude methiodide (2 g.) dissolved in water, and excess of dilute sodium hydroxide solution added. The liberated base was extracted with ether, the ethereal layer dried, and the solvent removed. Distillation of the residue gave 1 : 2 : 3-trimethylpyrrocoline (0·1 g.) as a viscous yellow oil, b. p. 150°/15 mm. (bath-temp.), m. p. 12—13° (Found : C, 83·1; H, 8·4; N, 8·3. Calc. for $C_{11}H_{13}N$: C, 83·0; H, 8·2; N, 8·8%). The perchlorate formed prisms, m. p. and mixed m. p. 126—128°.

1-Dimethylaminomethyl-2 : 3-dimethylpyrrocoline.—A mixture of 30% aqueous dimethylamine (16·3 g., 1·05 mols.) and glacial acetic acid (14·5 g., 2·33 mols.) was cooled in an ice-bath. When the temperature had fallen to 5°, 40% aqueous formaldehyde (7·9 g., 1·0 mol.) was added. The resulting mixture was cooled to 5° and added to 2 : 3-dimethylpyrrocoline (15 g.). The mixture was shaken gently until it became homogeneous, set aside at room temperature for 45 hr., and then poured into a solution of sodium hydroxide (14·5 g.) in water (100 c.c.). The oil which separated was extracted with ether, the ethereal extracts were washed exhaustively with 2N-hydrochloric acid, and the combined acid extracts made alkaline by the addition of an excess of 2N-sodium hydroxide. The liberated base was extracted with ether, and the ethereal layer dried and concentrated. The yellow prisms which separated were collected, washed with ether, and crystallised from light petroleum (b. p. 60—80°), giving *di-(2 : 3-dimethyl-1-pyrrocolinyl)methane* (0·35 g.) as yellow needles, m. p. 109—110° (Found : C, 83·2; H, 7·4; N, 9·4. $C_{21}H_{22}N_2$ requires C, 83·5; H, 7·3; N, 9·3%).

A further amount (2·5 g.) of less pure di-(2 : 3-dimethyl-1-pyrrocolinyl)methane was obtained on removal of the solvent from the ethereal extracts which had been washed with hydrochloric acid. A small amount of the pure base was triturated with a few drops of 60% aqueous perchloric acid, and ether was added to complete the precipitation. The colourless *diperchlorate* which separated was washed thoroughly with ether and dried in a vacuum-desiccator; it had m. p. 179—181° (decomp.) (Found : C, 50·3; H, 5·0. $C_{21}H_{24}O_8N_2Cl_2$ requires C, 50·1; H, 4·8%). This compound decomposed on crystallisation from water or methanol.

The ethereal filtrate after removal of di-(2 : 3-dimethyl-1-pyrrocolinyl)methane was concentrated and the residue (11 g.) distilled; *1-dimethylaminomethyl-2 : 3-dimethylpyrrocoline* (5·3 g.) was obtained as pale yellow oil, b. p. 85—92°/0·05 mm., which on exposure to air and light became dark brown (Found : C, 77·1; H, 9·1; N, 13·9. $C_{13}H_{18}N_2$ requires C, 77·2; H, 8·9; N, 13·9%). In concentrated ethanolic solution it gave a *picrate* as a red microcrystalline solid, sintering at 133°, m. p. 137—139° (decomp.) (Found : C, 53·4; H, 4·9; N, 16·3. $C_{19}H_{21}O_7N_5$

requires C, 52·9; H, 4·9; N, 16·2%). An attempt was made to crystallise the picrate from benzene, but decomposition occurred and the picrate of dimethylamine was isolated as golden-yellow rhombs, m. p. 155·5—156·5° (reported m. p. 156°) (Found: C, 35·2; H, 3·7; N, 20·4. Calc. for $C_8H_{10}O_7N_4$: C, 35·0; H, 3·7; N, 20·4%).

Di-(2 : 3-dimethyl-1-pyrrocolinyl)methane.—Formaldehyde (40% aqueous; 2 g.) was added to a solution of 2 : 3-dimethylpyrrocoline (2·5 g.) in ethanol (20 c.c.) and concentrated hydrochloric acid (1 c.c.), kept for 4 hr., and then basified with dilute sodium hydroxide solution. The yellow needles which separated were collected, washed with ether, and recrystallised from light petroleum (b. p. 60—80°); di-(2 : 3-dimethyl-1-pyrrocolinyl)methane (2·0 g., 76·8%) was obtained as yellow needles, m. p. 109—110°, undepressed on admixture with a sample obtained as above. The identity of the product was confirmed by the m. p. of the perchlorate.

1-Methoxymethyl-2 : 3-dimethylpyrrocoline.—Freshly distilled 1-dimethylaminomethyl-2 : 3-dimethylpyrrocoline (0·5 g.) was added to a cooled solution of sodium (0·18 g.) in methanol (10 c.c.). After the addition of methyl iodide (1·05 g.), a stream of dry nitrogen was passed for 24 hr. through the solution. The tetramethylammonium iodide which separated from the reaction mixture was removed by filtration, the alcoholic filtrate poured into water and extracted with ether, and the ethereal layer separated and dried. The solvent was removed and the brown oil which remained was distilled. *1-Methoxymethyl-2 : 3-dimethylpyrrocoline* (0·15 g.) was obtained as a pale yellow oil (which became dark brown in air and light), b. p. 110°/0·05 mm. (bath-temp.) (Found: C, 76·1; H, 7·8. $C_{12}H_{15}ON$ requires C, 76·2; H, 7·9%)

1-Cyanomethyl-2 : 3-dimethylpyrrocoline.—Potassium cyanide (5·5 g.) in water (60 c.c.) was added to a mixture of freshly distilled 1-dimethylaminomethyl-2 : 3-dimethylpyrrocoline (6·5 g.), methyl iodide (13·65 g.), and ethanol (100 c.c.). A stream of dry nitrogen was passed through the reaction mixture for 24 hr. The pale yellow needles which separated were collected, and washed once with ethanol, and then thoroughly with water. Recrystallisation from light petroleum (b. p. 40—60°) gave *1-cyanomethyl-2 : 3-dimethylpyrrocoline* (2 g.) as pale yellow needles m. p. 78—79° (Found: C, 78·4; H, 6·6. $C_{12}H_{12}N_2$ requires C, 78·3; H, 6·5%). A further amount (0·5 g.) of the nitrile was obtained on removal of the ethanol from the mother-liquors. In the infra-red region the nitrile band is at 4·48 μ.

1 : 2-Dimethylpyrrocoline.—A mixture of 2-ethylpyridine (10·7 g.) and chloroacetone (9·3 g.) was heated on a steam-bath for 3 hr. and allowed to cool. The resulting brown solid was washed with ethanol–ether (1 : 1; 20 c.c.) and dissolved in distilled water (400 c.c.). Sodium hydrogen carbonate (25 g.) was added to the solution, which was heated on a steam-bath for 1 hr., and then distilled in steam. The cream-coloured solid which separated from the aqueous distillate was extracted with ether, the ethereal layer was dried, and the solvent removed. *1 : 2-Dimethylpyrrocoline* (8 g., 55%) was purified by sublimation at 100°/20 mm., and obtained as colourless plates with a blue fluorescence, m. p. 57—58° (Found: C, 82·6; H, 7·6; N, 9·6. $C_{10}H_{11}N$ requires C, 82·8; H, 7·6; N, 9·6%). The *perchlorate* was obtained from methanol as colourless rhombs with a slight pink tinge, m. p. 128—129° (sintering at 125°) (Found: C, 48·8; H, 5·0. $C_{10}H_{12}O_4NCl$ requires C, 48·9; H, 4·9%). The *picrate* was obtained from ethanol as yellow rhombs, m. p. 130—132° (decomp.) (Found: C, 51·4; H, 3·9. $C_{16}H_{14}O_7N_4$ requires C, 51·3; H, 3·7%).

2-Ethylpyrrocoline.—A mixture of α-picoline (10 g.) and bromomethyl ethyl ketone (16·4 g.) was heated on the water-bath for 2 hr. and then cooled. The solid quaternary salt which separated was washed once with ethanol–ether (1 : 1; 50 c.c.). The crude product was dissolved in water (200 c.c.), sodium hydrogen carbonate (20 g.) was added, and the mixture was heated on the steam-bath for 1 hr. and then distilled in steam. The cream-coloured solid which separated from the distillate was collected and dissolved in ether, the solution dried, and the ether removed. The crude product (14·5 g., 93%) was purified by sublimation at 100°/20 mm., *2-ethylpyrrocoline* being obtained as colourless plates becoming dark brown in air and light, m. p. 41° (Found: C, 82·9; H, 7·6. $C_{10}H_{11}N$ requires C, 82·8; H, 7·6%). The *perchlorate* was obtained from methanol as pale blue needles, m. p. 121—123° to a blue liquid (Found: C, 48·5; H, 4·9; N, 5·8; Cl, 14·6. $C_{10}H_{12}O_4NCl$ requires C, 48·9; H, 4·9; N, 5·7; Cl, 14·5%). The *picrate*, prepared in ethanol, was obtained from ethanol as yellow plates, m. p. 104—105·5° (Found: C, 51·2; H, 4·0. $C_{16}H_{14}O_7N_4$ requires C, 51·3; H, 3·7%).

This work was carried out during the tenure of a Ministry of Education Grant (E. D. R.) and an I.C.I. Fellowship (J. E. S.).

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, July 21st*, 1953.]

737. *Triterpene Resinols and Related Acids. Part XXVII.* Oleana-9(11) : 13(18)-dienol and Oleana-9(11) : 18-dienol. The Conversion of β-Amyrin into Germanicol.*

By J. M. Beaton, J. D. Johnston, L. C. McKean, and F. S. Spring.

Oleana-9(11) : 13(18)-dienyl acetate (II; R = Ac) has been obtained by catalytic hydrogenolysis or stepwise reduction of dioxo-β-amyradienyl acetate (I; R = Ac). Lithium aluminium hydride reduces (I; R = Ac) to oleana-9(11) : 13(18)-diene-3 : 19-diol † (V; R = H), the mono- and di-acetates of which yield (II; R = Ac) on catalytic hydrogenolysis. By a stepwise series of reductions (I; R = Ac) has been converted into olean-9(11)-ene-3 : 19α-diol (XVII; R = H) and 18α-olean-9(11)-ene-3 : 19β-diol (XIX; R = H), the monoacetates of which give oleana-9(11) : 18-dienyl acetate (XVIII; R = Ac) on dehydration. Oleana-9(11) : 13(18)- and -9(11) : 18-dienyl acetates are isomerised by mineral acid to oleana-11 : 13(18)-dienyl acetate (III; R = Ac).

The conversion of β-amyrin into germanicol is described. Oxidation of the β-amyrin derivative 18α-olean-9(11)-ene-3 : 19β-diol 3-acetate (XIX; R = Ac) with hydrogen peroxide, followed by Wolff–Kishner reduction of the intermediate 11-oxo-18α-oleanane-3 : 19β-diol 3-acetate (XX; R = Ac), gives 18α-oleanane-3 : 19β-diol (XXI; R = H) previously obtained from lupeol by Ames, Davy, Halsall, and Jones (*J.*, 1952, 2868). Dehydration of the monoacetate (XXI; R = Ac) yields germanicyl acetate (XXII; R = Ac).

The formation of dioxo-β-amyradienyl acetate from derivatives of β-amyrin acetate by selenium dioxide oxidation is discussed.

The experiments described below were undertaken with the object of preparing the non-conjugated dienyl acetates, oleana-9(11) : 13(18)-, 9(11) : 18-, and -11 : 18-dienyl acetates † which are required for comparison with a non-conjugated dienyl acetate obtained from oxo-*iso*-β-amyradienyl acetate to be described in a later part of this Series. A method for the preparation of oleana-11 : 18-dienyl acetate has not yet been discovered but alternative methods for the preparation of the 9(11) : 18- and 9(11) : 13(18)-dienyl acetates are described below.

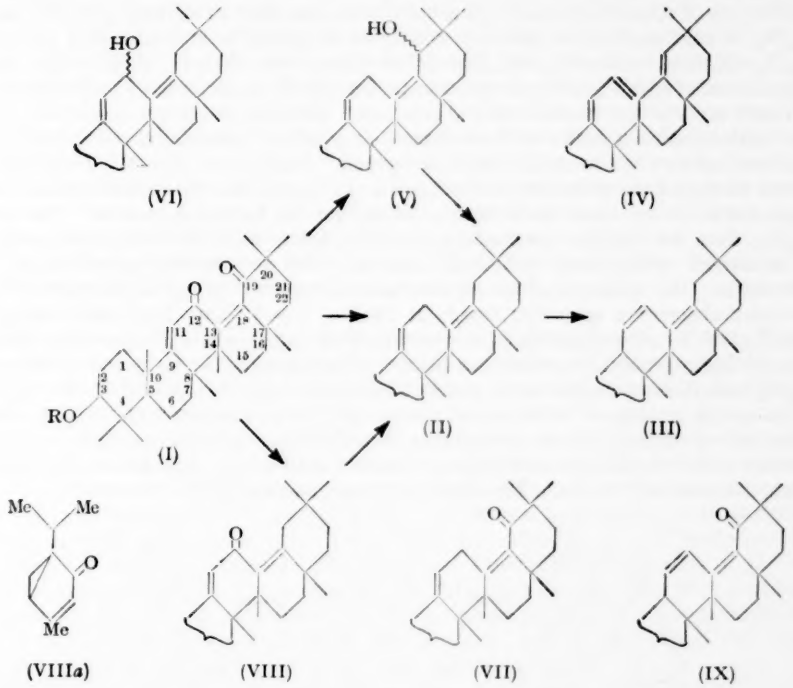
As a first approach to oleana-9(11) : 13(18)-dienyl acetate, the hydrogenolysis of dioxo-β-amyradienyl acetate (I) ‡ was examined. When platinum was used as catalyst and acetic acid as solvent two products, $C_{32}H_{50}O_2$ and $C_{32}H_{50}O_3$, were isolated. The former gives a deep yellow colour with tetranitromethane in chloroform, and shows an apparent absorption maximum at 2100 Å (ε = 10,000) but does not selectively absorb in the ultra-violet region above 2200 Å. When treated with hydrochloric–acetic acid, it is isomerised to oleana-11 : 13(18)-dienyl acetate (III) (Barton and Brooks, *J.*, 1951, 257) in high yield. The compound $C_{32}H_{50}O_2$ is therefore one of the three non-conjugated oleanadienyl acetates named in the first paragraph; its intense absorption of light between 2100 and 2250 Å (Bladon, Henbest, and Wood, *J.*, 1952, 2737; Halsall, *Chem. and Ind.*, 1951, 867), together with its method of preparation, suggests that one of the double bonds is between $C_{(13)}$ and $C_{(18)}$. Consequently we conclude that the compound is oleana-9(11) : 13(18)-dienyl acetate (II), a decision confirmed by its formation by another route to be described.

The second product of the catalytic hydrogenolysis of dioxo-β-amyradienyl acetate is 19-oxo-olean-9(11)-enyl acetate (XI) : it gives a yellow colour with tetranitromethane and its ultra-violet absorption spectrum indicates the presence of a triply substituted double bond and an isolated carbonyl group. 19-Oxo-olean-9(11)-enyl acetate has been obtained from dioxo-β-amyradienyl acetate by an unambiguous stepwise method described below.

Oleana-9(11) : 13(18)-dienyl acetate has also been prepared from dioxo-β-amyradienyl acetate by a two-stage reduction process. Treatment of the dioxodienyl acetate with

* Part XXVI, *J.*, 1953, 943. † For numbering [cf. (I)] see *J.*, 1953, 3024.
‡ Unless specified to the contrary, R = Ac in all the formulæ.

lithium aluminium hydride gives an oleanadienediol, $C_{30}H_{48}O_2$. This remarkable reaction has involved the reduction of one of the two carbonyl groups of the parent dioxodienyl acetate to a methylene group and the normal reduction of the second carbonyl to a secondary hydroxyl group. Partial acetylation of the diol yields a monoacetate, $C_{32}H_{50}O_3$, which gives a yellow colour with the tetranitromethane reagent. The monoacetate does not exhibit selective absorption in the ultra-violet region above 2200 Å but shows strong absorption between 2100 and 2250 Å similar to that of oleana-9(11) : 13(18)-dienyl acetate.

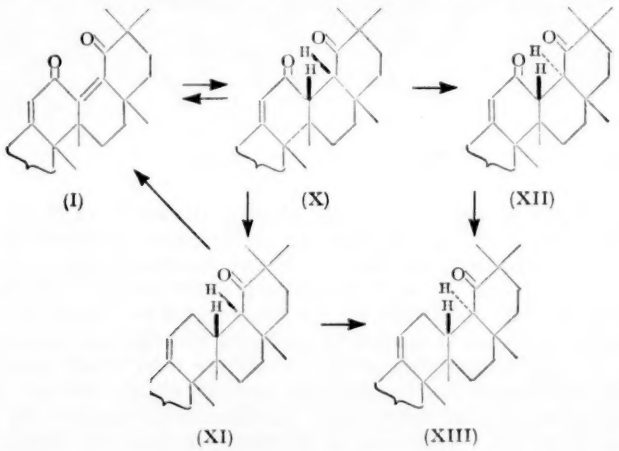


Prolonged acetylation of the monoacetate yields a diacetate, $C_{34}H_{52}O_4$, and catalytic hydrogenolysis of either the monoacetate or the diacetate yields oleana-9(11) : 13(18)-dienyl acetate. In order to decide between the two possible structures, (V) and (VI), for the monoacetate an attempt was made to oxidise it to the ketone; a decision between the alternative formulæ (VII) and (VIII) for the latter should be readily made. The ketone was not obtained; oxidation of the diol monoacetate with chromic acid equivalent to one oxygen atom at room temperature yielded a mixture from which dioxo-β-amyradienyl acetate (I) and unchanged diol monoacetate were separated; on use of an excess of oxidising agent, again at room temperature, the dioxodienyl acetate was isolated as sole product in excellent yield. Treatment of the diol diacetate with chromic acid at room temperature also gave the dioxodienyl acetate. Treatment of the monoacetate with mineral acid converts it in high yield into oleana-9(11) : 12 : 18-trienyl acetate (IV) (Ruzicka, Jeger, and Redel, *Helv. Chim. Acta*, 1943, **26**, 1235) presumably by anionotropic rearrangement and dehydration. It is probable that the oxidation of the monoacetate (and diacetate) is preceded by a similar conversion into the trienyl acetate, oxidation of which with chromic acid gives the dioxodienyl acetate (Newbold and Spring, *J.*, 1944, 532). An attempt to oxidise the diol monoacetate with manganese dioxide also led to the trienyl acetate.

Attention was next directed to the preparation of oleana-9(11) : 18-dienyl acetate.

Barton, Holness, Overton, and Rosenfelder (*J.*, 1952, 3751) observed that methyl 12 : 19-dioxo-oleana-9(11) : 13(18)-dienolate acetate * is reduced smoothly by zinc and acetic acid to methyl 12 : 19-dioxo-olean-9(11)-enolate acetate. Using their conditions we find that reduction of the related 12 : 19-dioxo-oleana-9(11) : 13(18)-dienyl acetate (dioxo-β-amyradienyl acetate) is a complex reaction, giving a mixture separated by chromatography into (*a*) oleana-9(11) : 13(18)-dienyl acetate (II) identical with the dienyl acetate obtained from dioxo-β-amyradienyl acetate by the two methods described above, (*b*) an acetate, $C_{32}H_{48}O_3$, and (*c*) an acetate, $C_{32}H_{48}O_4$.

Reduction of dioxo-β-amyradienyl acetate with zinc dust in ethanol gives the acetate, $C_{32}H_{48}O_4$, as sole product in excellent yield; it is probably identical with an acetate, $C_{32}H_{48}O_4$, obtained by Ruzicka and Jeger (*Helv. Chim. Acta*, 1941, **24**, 1236) by the catalytic hydrogenation of dioxo-β-amyradienyl acetate for which the structure 12 : 19-dioxo-olean-13(18)-enyl acetate was considered and rejected. Ruzicka and Jeger suggested that the acetate may have been produced from dioxo-β-amyradienyl acetate by reduction of one of the carbonyl groups to a secondary hydroxyl group. Barton *et al.* (*loc. cit.*, 1952), however, preferred to regard the reduction product as 12 : 19-dioxo-olean-9(11)-enyl acetate (X) and this opinion is, in our view, undoubtedly correct for the following reasons. The acetate, $C_{32}H_{48}O_4$, does not contain a secondary hydroxyl group since it is recovered unchanged after treatment with acetic anhydride and is stable to chromic anhydride at room temperature. The presence of an αβ-unsaturated carbonyl group is established by the ultra-violet absorption spectrum (max. at 2460 Å, $\varepsilon = 12{,}500$), and the presence of a second (isolated) carbonyl group by conversion of the acetate into 19-oxo-olean-9(11)-enyl acetate by hydrogenolysis as described below. Consequently the formation of the acetate $C_{32}H_{48}O_4$ from dioxo-β-amyradienyl acetate has involved the reduction of the 13 : 18-double bond as in the analogous reduction of methyl 12 : 19-dioxo-olean-9(11) : 13(18)-dienolate acetate and as expected from mechanistic considerations (Barton *et al.*, *loc. cit.*, 1952). Treatment of 12 : 19-dioxo-olean-9(11)-enyl acetate with alkali, followed by reacetylation, gave the isomeric 12 : 19-dioxo-18α-olean-9(11)-enyl acetate (XII).



The differences between the products obtained from our catalytic reduction of dioxo-β-amyradienyl acetate and those obtained by Ruzicka and Jeger are to be attributed either to a difference in the activity of the platinum catalysts or to the incompleteness of the latter reaction since hydrogenolysis of 12 : 19-dioxo-olean-9(11)-enyl acetate using a platinum catalyst in acetic acid at room temperature yields 19-oxo-olean-9(11)-enyl acetate (XI) identical with the product obtained by direct hydrogenolysis of dioxo-β-amyradienyl acetate under the same conditions. The latter reaction, as shown above,

* Numbering as in this paper, not that of *J.*, 1952, 3751.

yields a mixture of oleana-9(11) : 13(18)-dienyl acetate (II) and 19-oxo-olean-9(11)-enyl acetate (XI). These two products are presumably formed by concurrent reactions, the latter as a result of saturation of the 13 : 18-double bond followed by hydrogenolysis of the 12-carbonyl group, and the former as a result of initial hydrogenolysis of one of the carbonyl groups to give 19- and/or 12-oxo-oleana-9(11) : 13(18)-dienyl acetate, further hydrogenolysis of which yields the 9(11) : 13(18)-dienyl acetate.

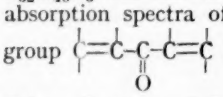
The acetate, $C_{32}H_{48}O_3$, obtained by zinc and acetic acid reduction of dioxo-β-amyradienyl acetate, gives a pale yellow colour with tetranitromethane, and its ultra-violet absorption spectrum shows intense maxima at 2080 ($\varepsilon = 9000$), 2600 ($\varepsilon = 9250$), and 2950 Å ($\varepsilon = 8450$). On catalytic hydrogenolysis it is converted in high yield into oleana-9(11) : 13(18)-dienyl acetate and on oxidation with selenium dioxide is converted into dioxo-β-amyradienyl acetate. Furthermore, during an attempt to convert it into an enol acetate by prolonged refluxing with acetic anhydride and sodium acetate, it was oxidised to dioxo-β-amyradienyl acetate. Because of its remarkable ultra-violet absorption spectrum, considerable pains were taken to ensure its homogeneity; on alkaline hydrolysis it gives a well-defined alcohol $C_{30}H_{46}O_2$, showing essentially the same ultra-violet absorption spectrum as the parent acetate. Reacetylation of the alcohol yields the acetate, $C_{32}H_{48}O_3$, with unaltered physical characteristics. This acetate is an intermediate in the conversion of dioxo-β-amyradienyl acetate into oleana-9(11) : 13(18)-dienyl acetate by means of zinc and acetic acid since further treatment of the acetate $C_{32}H_{48}O_3$ with these reagents converts it into the dienyl acetate.

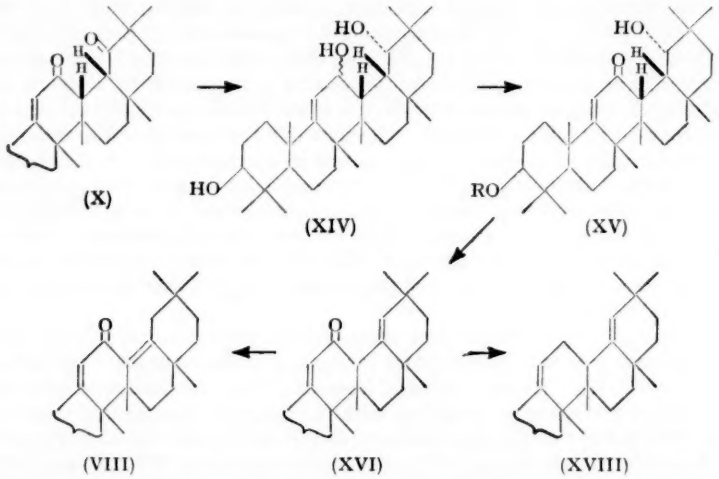
The acetate $C_{32}H_{48}O_3$ is formed from dioxo-β-amyradienyl acetate by the reduction of one of the carbonyl groups to a methylene group and is consequently to be formulated as either (VII) or (VIII). It was realised, however, that the nature of its ultra-violet absorption spectrum is roughly consistent with the view that the acetate is an inseparable mixture of (VII) and the conjugated dienone (IX), in which case the absorption maximum at 2600 Å is due to the αβ-unsaturated ketone chromophore of (VII) and the maximum at 2950 Å is attributable to the dienone chromophore of (IX). This view became improbable when the acetate was shown to be stable to strong mineral acid, and in particular when the ultra-violet absorption spectrum of the acetate was found to be unchanged after such treatment; if the mixed-crystal view is correct, mineral acid treatment of the acetate would be expected to yield the homogeneous conjugated dienone (IX) with a consequent change in the ultra-violet absorption spectrum. These considerations suggested that the acetate $C_{32}H_{48}O_3$ is 12-oxo-oleana-9(11) : 13(18)-dienyl acetate (VIII) and this has been confirmed by its partial synthesis by an unambiguous method.

Reduction of 12 : 19-dioxo-olean-9(11)-enyl acetate (X) with lithium aluminium hydride gives the unstable olean-9(11)-ene-3 : 12 : 19-triol (XIV) which may be a mixture of the 3 : 12α : 19α- and the 3 : 12β : 19α-triol. A differential oxidation of this triol was achieved by the use of manganese dioxide in acetone (Goodwin and Morton, *Biochem. J.*, 1948, **42**, 516) which oxidises αβ-unsaturated alcohols to the corresponding αβ-unsaturated carbonyl derivative (Attenburrow, Cameron, Chapman, Evans, Hems, Johnson, and Walker, *J.*, 1952, 1094) and is without effect, at room temperature, on saturated alcohols (Sondheimer and Rosenkranz, *Experientia*, 1953, **9**, 62). The triol (XIV) thus gave, on subsequent partial acetylation, 12-oxo-olean-9(11)-ene-3 : 19α-diol 3-acetate (XV), characterised as an αβ-unsaturated ketone by its ultra-violet absorption maximum at 2460 Å ($\varepsilon = 11{,}400$). Dehydration of 12-oxo-olean-9(11)-ene-3 : 19α-diol 3-acetate gave 12-oxo-oleana-9(11) : 18-dienyl acetate (XVI) which shows an ultra-violet absorption maximum at 2500 Å ($\varepsilon = 11{,}000$) and, unlike the parent 12-oxo-olean-9(11)-ene-3 : 19α-diol 3-acetate, gives a yellow colour with tetranitromethane. Treatment of 12-oxo-oleana-9(11) : 18-dienyl acetate with mineral acid readily gave 12-oxo-oleana-9(11) : 13(18)-dienyl acetate (VIII) * identical with the acetate $C_{32}H_{48}O_3$ obtained by treatment of dioxo-β-amyradienyl acetate with zinc and acetic acid.

Our initial reluctance to accept the now established structure (VIII) for the acetate

* Unsuccessful attempts to isomerise methyl 12-oxo-olean-18-enolate acetate to methyl 12-oxo-olean-13(18)-enolate acetate have been reported (Barton *et al.*, *loc. cit.*, 1952).

$C_{32}H_{48}O_3$ was due to its remarkable ultra-violet absorption spectrum. The ultra-violet absorption spectra of a number of conjugated dienones containing the chromophoric group  have been recorded (see, for example, the discussion by Ruzicka, Cohen, Furter, and Sluys-Veer, *Helv. Chim. Acta*, 1938, **21**, 1735). The acyclic phorone shows a single absorption maximum at 2650 Å in alcohol whilst cyclic dienones of this type

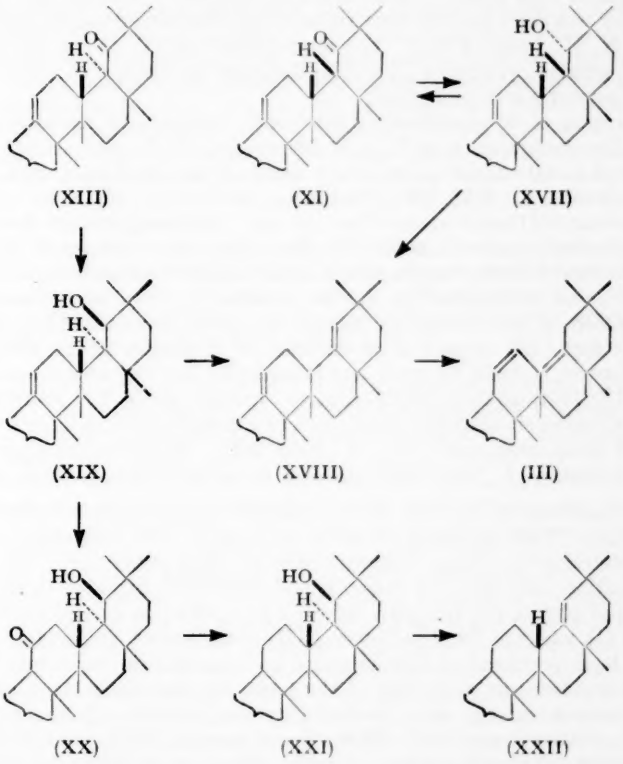


which contain the chromophore in a single six-membered ring (*e.g.*, steroid 1 : 4-dien-3-ones) show an intense absorption maximum at approx. 2400 Å. A dienone strictly analogous to 12-oxo-oleana-9(11) : 13(18)-dienyl acetate in which the chromophore is spread over two rings does not appear to have been described in either the steroid or the triterpenoid groups. It is probable that the abnormal absorption spectrum of 12-oxo-oleana-9(11) : 13(18)-dienyl acetate is to be associated with the distorted geometry of the chromophoric group. A resemblance in the shape of the absorption spectra curves for this acetate and for umbellulone (VIII*a*) is worthy of comment : the latter is also anomalous, with two maxima at 2200 ($\varepsilon = 5000$) and 2650 Å ($\varepsilon = 2900$) (Gillam and West, *J.*, 1945, 97), and this has been attributed to the distorted geometry of the total chromophore.

The establishment of the structure of the acetate $C_{32}H_{48}O_3$ as 12-oxo-oleana-9(11) : 13(18)-dienyl acetate has permitted a decision to be made between the alternative formulæ (V) and (VI) for the oleana-9(11) : 13(18)-diol monoacetate obtained from dioxo-β-amyradienyl acetate by lithium aluminium hydride reduction followed by partial acetylation. Reduction of 12-oxo-oleana-9(11) : 13(18)-dienyl acetate with lithium aluminium hydride (followed by acetylation) gives oleana-9(11) : 13(18)-dienyl acetate, reduction of the 12-carbonyl to a methylene group having occurred. This is similar to the reduction of dioxo-β-amyradienyl acetate with the same reagent and it is probable that the same carbonyl group has been involved in each case. If this is true, the diol monoacetate obtained from dioxo-β-amyradienyl acetate is oleana-9(11) : 13(18)-diene-3 : 19-diol 3-acetate (V).

Treatment of 19-oxo-olean-9(11)-enyl acetate (XI) with alkali followed by acetylation gives 19-oxo-18α-olean-9(11)-enyl acetate (XIII), also obtained, but not without difficulty, by hydrogenolysis of 12 : 19-dioxo-18α-olean-9(11)-enyl acetate (XII). These reactions prove that 19-oxo-olean-9(11)-enyl acetate and its alkali-stable isomer have the same configuration at $C_{(13)}$, that they differ solely in orientation around $C_{(18)}$, and that a similar relation obtains for the two isomeric 12 : 19-dioxo-olean-9(11)-enyl acetates.

Reduction of 19-oxo-18α-olean-9(11)-enyl acetate (XIII) with lithium aluminium hydride yields 18α-olean-9(11)-en-3 : 19β-diol, readily converted into the 3-monoacetate (XIX) by partial acetylation. Dehydration of the diol monoacetate with phosphorus oxychloride in pyridine yielded the required oleana-9(11) : 18-dienyl acetate (XVIII)



which does not show selective absorption in the ultra-violet region above 2200 Å. Treatment of the 9(11) : 18-dienyl acetate with hydrochloric–acetic acid converted it into oleana-11 : 13(18)-dienyl acetate (III). Reduction of 19-oxo-olean-9(11)-enyl acetate (XI) with lithium aluminium hydride gave olean-9(11)-ene-3 : 19α-diol, characterised as its 3-monoacetate (XVII) oxidation of which with chromic anhydride yielded the parent 19-ketone (XI). Dehydration of the diol monoacetate (XVII) with phosphorus oxychloride in pyridine again gave oleana-9(11) : 18-dienyl acetate (XVIII). Oleana-9(11) : 18-dienyl acetate (XVIII) is also obtained by catalytic hydrogenolysis of 12-oxo-oleana-9(11) : 18-dienyl acetate (XVI).

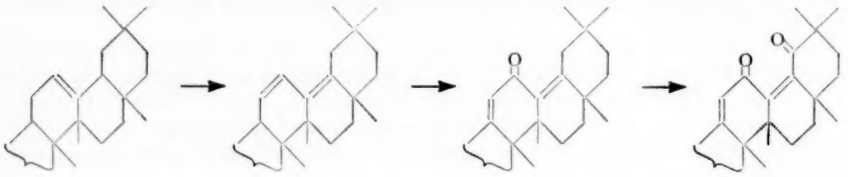
The conversion of 19-oxo-olean-9(11)-enyl acetate and its alkali-stable isomer into oleana-9(11) : 18-dienyl acetate again proves that the ketones have the same configuration at $C_{(13)}$. The configurations assigned to the 19-hydroxyl group in olean-9(11)-ene-3 : 19-diol 3-acetate and the 18α-isomer follow from the ease of dehydration with phosphorus oxychloride which requires a *trans*-arrangement of the hydrogen attached to $C_{(18)}$ and the $C_{(19)}$-hydroxyl group in each case.

The conversion of dioxo-β-amyradienyl acetate (readily available from β-amyrin) into olean-9(11)-ene-3 : 19α-diol 3-acetate (XVII) and 18α-olean-9(11)-ene-3 : 19β-diol 3-acetate (XIX) suggested a method for the direct inter-relation of the two naturally occurring triterpenoid alcohols, β-amyrin and germanicol, and this has been achieved starting from

(XIX); the 18α-isomer was chosen since this leads at an earlier stage to a known intermediate.

Oxidation of the unsaturated diol monoacetate (XIX) with hydrogen peroxide in acetic acid gave the expected 11-oxo-18α-oleanane-3 : 19β-diol 3-acetate (XX), Wolff–Kishner reduction of which gave 18α-oleanane-3 : 19β-diol (XXI; R = H) identical with a specimen prepared from lupeol as described by Ames, Davy, Halsall, and Jones (*J.*, 1952, 2868); identity was confirmed by a mixed melting point determination kindly effected by Professor E. R. H. Jones, F.R.S. The monoacetate (XXI) of the diol was converted smoothly into germanicyl acetate (XXII) as described by Ames *et al.*, thus completing the conversion of β-amyrin into germanicol.

The conversion of 19-oxo-18α-olean-9(11)-enyl acetate into 18α-oleanane-3 : 19β-diol proves that the configuration at $C_{(13)}$ in 19-oxo-olean-9(11)-enyl acetate, 12 : 19-dioxo-olean-9(11)-enyl acetate and its alkali-stable isomer is the same (β) as that in morolic acid (Barton and Brooks, *J.*, 1951, 257; Barton and Holness, *J.*, 1952, 78). It follows that 12 : 19-dioxo-olean-9(11)-enyl acetate has the 13β : 18β-configuration shown in (X) and that the alkali-stable isomer has the 13β : 18α-configuration shown in (XII). Thus the zinc dust reduction of dioxo-β-amyradienyl acetate involves *cis*-addition of hydrogen to the 13 : 18-double bond, as assumed by Barton, Holness, Overton, and Rosenfelder (*loc. cit.*) for the reduction of the analogous methyl 12 : 19-dioxo-oleana-9(11) : 13(18)-dienolate acetate. The first case of such a *cis*-addition of hydrogen to an ene-1 : 4-dione was reported by Barton, Holness, Overton, and Rosenfelder (*loc. cit.*) who showed that reduction of methyl 12 : 19-dioxo-olean-13(18)-enolate acetate gives 12 : 19-dioxo-oleananolate acetate, and a similar *cis*-addition of hydrogen to a steroid ene-1 : 4-dione has subsequently been reported (Budziarek and Spring, *J.*, 1953, 956). Recently, the elegant experiments of Barnes and Barton (*J.*, 1953, 1419) have led to the generalisation that selenium dioxide oxidation of anediones of the type $-CO\cdot\overset{|}{C}H\cdot\overset{|}{C}H\cdot CO-$ to the enedione $-CO\cdot\overset{|}{C}{:}\overset{|}{C}\cdot CO$ requires a *cis*-arrangement of the hydrogen atoms in the former. We are grateful to Dr. D. H. R. Barton for informing us of these observations before their publication. In agreement with this generalisation and with the stereochemical relations deduced above, 12 : 19-dioxo-olean-9(11)-enyl acetate (X) is readily oxidised with selenium dioxide to dioxo-β-amyradienyl acetate (I) whereas the 18α-isomer (XII) is recovered unchanged after the same treatment. It is pertinent at this juncture to comment on the formation of dioxo-β-amyradienyl acetate from a number of the β-amyrin derivatives described above. This acetate is obtained, among other methods, by the oxidation of 19-oxo-olean-9(11)-enyl acetate (XI), 12-oxo-oleana-9(11) : 13(18)-dienyl acetate (VIII), and 12 : 19-dioxo-olean-9(11)-enyl acetate (X) with selenium dioxide. In a recent discussion, Barton, Holness, Overton, and Rosenfelder (*loc. cit.*) observed that the dioxodienyl acetate is never produced if substituents containing oxygen are already present even at $C_{(12)}$ and/or $C_{(19)}$. This view must now be abandoned although the corollary that selenium dioxide oxidations of -enes and -dienes (in which the double bonds are in the fragment $C_{(10)}$–$C_{(19)}$) to the dienedione system proceed *via* the 9(11) : 12 : 18-triene may still be true. An alternative hypothesis is that at least some of these oxidations proceed *via* the 12-oxo-9(11) : 13(18)-diene without the intervention of the 9(11) : 12 : 18-triene, as exemplified below for β-amyrin acetate.



The fact that the 12-oxo-9(11) : 13(18)-diene has not been isolated as an intermediate oxidation product is explained as in the case of the 9(11) : 12 : 18-triene hypothesis, by its relative ease of oxidation to the dioxodienyl acetate.

Experimental

Rotations were measured in chloroform solution at approx. 15°, and ultra-violet absorption spectra were measured in ethanol solutions with a Unicam SP. 500 spectrophotometer. Grade II alumina and a light petroleum fraction of b. p. 60—80° were used for chromatography.

Catalytic Hydrogenolysis of Dioxo-β-amyradienyl Acetate.—A solution of dioxo-β-amyradienyl acetate (1·27 g.) in glacial acetic acid (120 c.c.) was shaken with hydrogen and platinum (from 0·5 g. of PtO_2) for 48 hr. Hydrogen absorption (approx. 4 mols.) had then ceased and crystalline solid had separated. The product was isolated in the usual way, and chromatographed in light petroleum (100 c.c.) on alumina (12 × 2 cm.). Light petroleum (60 c.c.) and light petroleum–benzene (1 : 1; 100 c.c.) eluted a solid (400 mg.) which after four crystallisations from methanol–chloroform gave *oleana*-9(11) : 13(18)-*dienyl acetate* as plates, m. p. 198·5—200·5°, $[\alpha]_D$ +60°, +59·5° (*c*, 1·3, 1·0) (Found: C, 82·6; H, 11·1. $C_{32}H_{50}O_2$ requires C, 82·3; H, 10·8%). Light absorption: ε_{2100} = 10,000, ε_{2150} = 9000, ε_{2220} = 5600. *Oleana*-9(11) : 13(18)-*dienol*, obtained by hydrolysis of the acetate with 4% ethanolic potassium hydroxide, separates from methanol as needles, m. p. 204·5—206·5°, $[\alpha]_D$ +53·5°, +52° (*c*, 0·5, 0·9) (Found: C, 84·9; H, 11·5. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%).

Continued elution of the alumina with benzene (300 c.c.) gave a crystalline solid (250 mg.) which after five crystallisations from methanol–chloroform gave 19-*oxo-olean*-9(11)-*enyl acetate* as plates, m. p. 254—256°, $[\alpha]_D$ +117·5°, +116° (*c*, 1·15, 1·0) (Found: C, 79·9; H, 10·4. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·4%). It gives a pale yellow colour with tetranitromethane in chloroform. Light absorption: Max. at 3020 Å (ε = 44); ε_{2060} = 3400, ε_{2100} = 2400, ε_{2150} = 920.

Further elution of the alumina column gave fractions which could not be adequately purified but which did not show intense selective absorption in the ultra-violet above 2200 Å.

Conversion of Oleana-9(11) : 13(18)-*dienyl Acetate into Oleana*-11 : 13(18)-*dienyl Acetate.*—A solution of oleana-9(11) : 13(18)-dienyl acetate (87 mg.) in acetic acid (15 c.c.) containing concentrated hydrochloric acid (1·5 c.c.) was heated for 3 hr. on the steam-bath. The product, isolated by means of ether, was treated with acetic anhydride (1 c.c.) and pyridine (1 c.c.). Crystallisation of the acetylated product from methanol–chloroform gave oleana-11 : 13(18)-dienyl acetate (50 mg.) as plates, m. p. and mixed m. p. 223—226°, $[\alpha]_D$ −63° (*c*, 1·2). Light absorption: Max. at 2420 (ε = 23,500), 2500 (ε = 27,000), and 2600 Å (ε = 17,600).

Reduction of Dioxo-β-amyradienyl Acetate with Lithium Aluminium Hydride.—A solution of dioxo-β-amyradienyl acetate (2 g.) in dry ether (250 c.c.) was added to a suspension of lithium aluminium hydride (3 g.) in ether (400 c.c.), and the mixture heated under reflux for 4 hr. The product was isolated in the usual manner, mineral acid being avoided. A solution of the product in pyridine (50 c.c.) and acetic anhydride (25 c.c.) was kept overnight at room temperature and then heated on the water-bath for 1 hr. The crude product is probably contaminated with β-amyratrienyl acetate since it gives a red-brown colour with tetranitromethane and a broad absorption maximum at 3110 Å (ε = 1100). Seven crystallisations of the acetylated product from methanol gave *oleana*-9(11) : 13(18)-*diene*-3 : 19-*diol* 3-*acetate* as needles, m. p. 223—224°; the $[\alpha]_D$, +75° (*c*, 0·7), did not change during the last three crystallisations (Found: C, 79·35; H, 10·4. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·4%). It gives a yellow colour with tetranitromethane in chloroform and does not selectively absorb in the ultra-violet region above 2200 Å.

A solution of the monoacetate (300 mg.) in pyridine (10 c.c.) and acetic anhydride (10 c.c.) was kept at room temperature for 6 days. Crystallisation of the product from methanol gave *oleana*-9(11) : 13(18)-*diene*-3 : 19-*diol diacetate* as needles, m. p. 231—231·5°, $[\alpha]_D$ +60° (*c*, 0·8) (Found: C, 77·6; H, 10·1. $C_{34}H_{52}O_4$ requires C, 77·8; H, 10·0%). Light absorption: ε_{2100} = 11,800, ε_{2150} = 8900, ε_{2200} = 6000, ε_{2250} = 3200, ε_{2300} = 1100. The diacetate gives a yellow colour with tetranitromethane.

Oleana-9(11) : 13(18)-*diene*-3 : 19-*diol.*—A solution of the diol diacetate (200 mg.) in dry ether (200 c.c.) was treated with lithium aluminium hydride (200 mg.). After 1 hr. the product was isolated (the use of mineral acid being avoided) and crystallised from aqueous methanol from which *oleana*-9(11) : 13(18)-*diene*-3 : 19-*diol* separated as plates, m. p. 240—243°. Purification by recrystallisation from the same solvent was accompanied by a drop in m. p. to 230—231°, unaltered by further recrystallisation or by drying in a vacuum, $[\alpha]_D$ +58° (*c*, 0·5, 0·6) (Found: C, 81·5; H, 11·2. $C_{30}H_{48}O_2$ requires C, 81·8; H, 11·0%). Light absorption: ε_{2090} = 12,500, ε_{2150} = 10,000, ε_{2200} = 6300, ε_{2300} = 1200.

Oleana-9(11) : 12 : 18-*trienyl Acetate from Oleana*-9(11) : 13(18)-*diene*-3 : 19-*diol* 3-*Acetate.*—(*a*) A solution of the monoacetate (210 mg.) in acetic acid (25 c.c.) was treated with 3 drops of concentrated hydrochloric acid, and the solution kept at room temperature for 16 hr. It was

then heated on a steam-bath for 30 min. The product was isolated by means of ether and crystallised from chloroform–methanol, to yield oleana-9(11) : 12 : 18-trienyl acetate (175 mg.) as plates, m. p. 180—181°, $[\alpha]_D$ +570° (*c*, 1·0); it gives a deep brown colour with tetranitromethane in chloroform. Light absorption: Max. at 3100 Å (ε = 14,800). Ruzicka *et al.* (*loc. cit.*, 1943) give m. p. 185° (corr.), $[\alpha]_D$ +527°, max. at 3080 Å (log ε = 4·1), for β-amyratrienyl acetate; Newbold and Spring (*J.*, 1944, 532) give m. p. 184—185°, $[\alpha]_D$ +560°.

(*b*) The monoacetate (310 mg.) in acetone (100 c.c.) was shaken with freshly prepared manganese dioxide (10 g.) for 9 hr. The product isolated in the usual manner was crystallised from methanol, to give oleana-9(11) : 12 : 18-trienyl acetate (198 mg.), m. p. 179—183° and 180—181·5° after recrystallisation from the same solvent; $[\alpha]_D$ +545° (*c*, 1·5); Max. at 3100 Å (ε = 14,000); a mixture with an authentic specimen was undepressed in m. p.

Catalytic Hydrogenolysis of Oleana-9(11) : 13(18)-diene-3 : 19-diol Diacetate.—A solution of the diacetate (150 mg.) in glacial acetic acid (50 c.c.) was added to a suspension of platinum (from 100 mg. of PtO_2) in glacial acetic acid (20 c.c.), and the mixture shaken with hydrogen for 18 hr. The product crystallised from chloroform–methanol, to yield oleana-9(11) : 13(18)-dienyl acetate (100 mg.) as plates, m. p. 199—200°, $[\alpha]_D$ +58°, +59° (*c*, 0·8, 0·5) (Found: C, 82·2; H, 10·9. $C_{32}H_{50}O_2$ requires C, 82·3; H, 10·8%). Light absorption: ε_{2160} = 6200, ε_{2300} = 5600, ε_{2250} = 3300, ε_{2300} = 950. A mixture with a specimen prepared by the hydrogenolysis of dioxo-β-amyradienyl acetate was undepressed in m. p.

Similar hydrogenolysis of oleana-9(11) : 13(18)-diene-3 : 19-diol 3-acetate gave oleana-9(11) : 13(18)-dienyl acetate as plates (from chloroform–methanol), m. p. and mixed m. p. 198—200°, $[\alpha]_D$ +59° (*c*, 1·2).

Oxidation of Oleana-9(11) : 13(18)-diene-3 : 19-diol 3-Acetate with Chromic Acid.—(*a*) The diol monoacetate (500 mg.) in glacial acetic acid (100 c.c.) was treated with chromic acid (77 mg.) in water (1 c.c.) and acetic acid (24 c.c.) at room temperature, and the solution kept for 16 hr. It was heated on the water-bath for 15 min. and the product isolated in the usual manner. Crystallisation from methanol gave a less soluble fraction (210 mg.) as needles, m. p. 215—218°, recrystallisation of which gave the diol monoacetate, m. p. 221—223°, $[\alpha]_D$ +70° (*c*, 1·3), undepressed in m. p. when mixed with starting material. A more soluble fraction (160 mg.) separated as plates, m. p. 222—225°, $[\alpha]_D$ −62°, recrystallisation of which gave dioxo-β-amyradienyl acetate, m. p. 234—236°, undepressed when mixed with an authentic specimen and showing an absorption maximum at 2800 Å (ε = 10,000).

(*b*) Repetition of the experiment, but with chromic anhydride equivalent to 4O, gave dioxo-β-amyradienyl acetate, m. p. 239—240°, $[\alpha]_D$ −86° (*c*, 1·8), max. at 2780 Å (ε = 12,000), in nearly quantitative yield.

A similar oxidation of oleana-9(11) : 13(18)-diene-3 : 19-diol diacetate (325 mg.) with chromic acid equivalent to 2O in acetic acid at room temperature gave a mixture which was separated by chromatography on alumina into unchanged diol diacetate (23 mg.), needles (from methanol), m. p. 218—224° undepressed when mixed with starting material, and the more strongly absorbed dioxo-β-amyradienyl acetate (250 mg.) which separated from aqueous methanol as plates, m. p. and mixed m. p. 236—238°, $[\alpha]_D$ −87° (*c*, 0·9). Light absorption: Max. at 2760 Å (ε = 12,600).

Reduction of Dioxo-β-amyradienyl Acetate with Zinc and Acetic Acid.—A solution of dioxo-β-amyradienyl acetate (0·95 g.) in glacial acetic acid (100 c.c.) was gently refluxed for 4 hr. with zinc dust (1·8 g.). A solution of the product, isolated by means of ether, in light petroleum (100 c.c.) and benzene (40 c.c.) was chromatographed on alumina (15 × 1·5 cm.). The fraction (229 mg.; m. p. 190°) eluted with light petroleum–benzene (2 : 1, 200 c.c.; then 1 : 1, 300 c.c.) was crystallised thrice from methanol–chloroform, to give oleana-9(11) : 13(18)-dienyl acetate as plates, $[\alpha]_D$ +60° (*c*, 1·0), m. p. 195—197° alone or mixed with the specimen described above.

A fraction (28 mg.) obtained by continued washing of the alumina column with benzene–light petroleum (3 : 2; 100 c.c.) was not examined. The fractions obtained by washing the column with benzene (300 c.c.), benzene–ether (9 : 1, 200 c.c.; then 4 : 1, 50 c.c.) were combined (314 mg.; m. p.s 204° to 207°) and crystallised from aqueous methanol from which the *12-oxo-oleana-9(11) : 13(18)-dienyl acetate* separated as plates from concentrated solution and as prisms from dilute solution; these had m. p. 205—207°, $[\alpha]_D$ −79°, −78° (*c*, 1·0, 0·9) (Found: C, 79·95; H, 10·3. $C_{32}H_{48}O_3$ requires C, 79·95; H, 10·1%). Light absorption: Max. at 2080 (ε = 9000), 2600 (ε = 9250), and 2950 Å (ε = 8450).

A fraction (157 mg.; m. p. 280—287°) obtained by washing the alumina column with benzene–ether (3 : 2, 50 c.c.; then 1 : 1, 100 c.c.; then 2 : 3, 50 c.c.) and ether (200 c.c.) crystallised from aqueous methanol, to yield *12 : 19-dioxo-olean-9(11)-enyl acetate* as plates, m. p. 285—

287°, $[\alpha]_D$ +132° (*c*, 1·0) (Found: C, 77·6; H, 9·9. $C_{32}H_{48}O_4$ requires C, 77·4; H, 9·7%). Light absorption: Max. at 2460 Å (ε = 12,400). Ruzicka and Jeger (*loc. cit.*) give m. p. 290—292° (corr.), $\lambda_{max.}$ at 2400 Å (log ε = 4·05), for a compound $C_{32}H_{48}O_4$ obtained by catalytic reduction of dioxo-β-amyradienyl acetate.

12-*Oxo-oleana*-9(11) : 13(18)-*dienol* was obtained when the corresponding acetate was heated with 3% alcoholic potassium hydroxide for 3 hr. It separated from aqueous methanol as needles, m. p. 267—269°, $[\alpha]_D$ −99·5°, −100°, −99° (*c*, 1·1, 0·75, 0·8) (Found: C, 82·3; H, 10·7. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·6%). Light absorption: Max. at 2100 (ε = 7600), 2620 (ε = 8600), and 2950 Å (ε = 7900). Reacetylation (pyridine–acetic anhydride) of the alcohol gave 12-oxo-oleana-9(11) : 13(18)-dienyl acetate as prisms or plates (from aqueous methanol), m. p. 205—206°, $[\alpha]_D$ −78° (*c*, 1·35). The acetate (125 mg.) was recovered unchanged [m. p. 204—205°, $[\alpha]_D$ −78° (*c*, 1·1). Light absorption: Max. at 2080 (ε = 7250), 2600 (ε = 8950) and 2950 Å (ε = 8100)] after being heated on a steam-bath for 3 hr. with acetic acid (25 c.c.) and concentrated hydrochloric acid (3 c.c.).

Reduction of 12-*Oxo-oleana*-9(11) : 13(18)-*dienyl Acetate*.—(a) *Catalytic*. A solution of the acetate (0·3 g.) in acetic acid (50 c.c.) was shaken with platinum (from 0·2 g. of PtO_2) and hydrogen for 7 hr. Towards the end of the reaction the product separated from the solution. Oleana-9(11) : 13(18)-dienyl acetate, isolated by means of ether, crystallised from methanol–chloroform as plates (250 mg.), m. p. 197—199°, $[\alpha]_D$ +59° (*c*, 0·9); the m. p. of a mixture with the specimen described above was undepressed.

(b) *With zinc and acetic acid*. A solution of the acetate (250 mg.) in glacial acetic acid (50 c.c.) was refluxed with zinc (0·5 g.) for 4 hr. The product was isolated by means of ether and crystallised from chloroform–methanol to yield the relatively insoluble oleana-9(11) : 13(18)-dienyl acetate (50 mg.) as plates, m. p. 190—191°. The mother-liquor was evaporated to dryness, the residue dissolved in glacial acetic acid, and the solution again refluxed with zinc (0·5 g.) for 4 hr. The product was isolated by means of ether and crystallised from chloroform–methanol, to yield oleana-9(11) : 13(18)-dienyl acetate (58 mg.) as plates, m. p. 188—190°. Recrystallisation of the combined crops from chloroform–methanol yielded the dienyl acetate as plates, m. p. and mixed m. p. 196—198°.

(c) *With lithium aluminium hydride*. A solution of the acetate (1·0 g.) in dry ether (250 c.c.) containing lithium aluminium hydride (1·0 g.) was refluxed for 3 hr. The product was isolated, the use of mineral acid being avoided, and acetylated with pyridine and acetic anhydride at room temperature. The acetylated product crystallised from methanol–chloroform to give a mixture (approx. 500 mg.), m. p. 192—194°. This gives a brown colour with tetranitromethane and shows an absorption maximum at 2950 Å (ε = 440) probably due to the presence of oleana-9(11) : 12 : 18-trienyl acetate. Recrystallisation of this solid from chloroform–methanol, which was accompanied by large losses, gave oleana-9(11) : 13(18)-dienyl acetate (50 mg.) as plates, m. p. and mixed m. p. 199—200°, giving a yellow colour with tetranitromethane; $[\alpha]_D$ was +59° (*c*, 0·9, 1·0). Light absorption: Max. at 2100 Å (ε = 8000).

Dioxo-β-amyradienyl Acetate from 12-*Oxo-oleana*-9(11) : 13(18)-*dienyl Acetate*.—(*a*) The acetate (86 mg.) was refluxed for 72 hr. with acetic anhydride (10 c.c.) containing freshly fused potassium acetate (0·1 g.). The product was isolated in the usual manner and crystallised from methanol, to yield dioxo-β-amyradienyl acetate (50 mg.) as plates, m. p. and mixed m. p. 241—242°, $[\alpha]_D$ −89° (*c*, 0·6). Light absorption: Max. at 2780 Å (ε = 11,000).

(*b*) The acetate (250 mg.) in glacial acetic acid (50 c.c.) was refluxed with selenium dioxide (250 mg.) for 6 hr. Crystallisation of the product from aqueous methanol yielded dioxo-β-amyradienyl acetate (130 mg.) as large plates, m. p. and mixed m. p. 240—241°, $[\alpha]_D$ −91° (*c*, 1·3). Light absorption: Max. at 2760 Å (ε = 12,500).

Reduction of Dioxo-β-amyradienyl Acetate with Zinc Dust in Ethanol.—A solution of the dioxodienyl acetate (5 g.) in boiling ethanol (500 c.c.) was refluxed with freshly activated zinc dust (25 g.) for 5 hr. The product was crystallised from methanol–chloroform, to yield 12 : 19-dioxo-olean-9(11)-enyl acetate (4·5 g.) as blades, m. p. 287—290°, (decomp.), $[\alpha]_D$ +135°, +132° (*c*, 1·4, 1·3), undepressed in m. p. when mixed with the specimen described above. 12 : 19-Dioxo-olean-9(11)-enyl acetate was recovered unchanged after 1 hr.' heating on the water-bath with acetic anhydride and pyridine, also after being kept overnight in glacial acetic acid containing chromic acid (equiv. to 1O).

12-*Oxo-olean*-9(11)-*ene*-3 : 19α-*diol* 3-*Acetate from* 12 : 19-*Dioxo-olean*-9(11)-*enyl Acetate*.—A solution of 12 : 19-dioxo-olean-9(11)-enyl acetate (2·0 g.) in benzene (150 c.c.) was added to a suspension of lithium aluminium hydride (2·0 g.) in ether (1 l.). After the mixture had been shaken for 1 hr. at room temperature the excess of hydride was decomposed by the addition of

ice. The solution was washed with water, dried, and concentrated to 40 c.c. Crude olean-9(11)-ene-3 : 12 : 19-triol separated as needles, m. p. 210—230°. A second experiment gave a product which separated from acetone–light petroleum as fine matted needles, m. p. 220—224°. Attempted purification by crystallisation was not successful, the m. p. falling to 183—185°. In a third experiment the product was not obtained crystalline. Each of these specimens, however, was essentially the required triol since each was successfully converted in high yield into 12-oxo-olean-9(11)-ene-3 : 19α-diol 3-acetate as described below. The crude triol did not show appreciable selective absorption above 2200 Å.

A solution of the crude triol (1·8 g.) in acetone (150 c.c.) was shaken with freshly precipitated, dry manganese dioxide (20 g.) for 17 hr. The product recovered in the usual manner showed an absorption maximum at 2480 Å ($\varepsilon = 7200$). It was again dissolved in acetone and shaken with manganese dioxide (20 g.) for 17 hr.; the absorption spectrum of the product then showed a maximum at 2480 Å ($\varepsilon = 8500$). The crude product was partially acetylated by treatment in acetic anhydride (25 c.c.) and pyridine (50 c.c.) at room temperature. After 13 hr. the acetylated product was isolated in the usual manner and crystallised from aqueous methanol from which *12-oxo-olean-9(11)-ene-3 : 19α-diol 3-acetate* (0·72 g.) separated as prismatic needles, m. p. 266—267°, $[\alpha]_D$ +97° (*c*, 1·45) (Found: C, 77·4; H, 10·2. $C_{32}H_{50}O_4$ requires C, 77·1; H, 10·1%). Light absorption: Max. at 2460 Å ($\varepsilon = 11{,}400$). Chromatography of solid recovered from the aqueous-methanolic mother-liquors gave a further quantity (0·22 g.) of this acetate, m. p. 266—267°.

Dehydration of 12-Oxo-olean-9(11)-ene-3 : 19α-diol 3-Acetate.—A solution of the diol monoacetate (450 mg.) in pyridine (50 c.c.) was treated with phosphorus pentachloride (2 g.) and kept in nitrogen for 17 hr. at room temperature. The mixture was diluted with water, the solid collected and washed with water, and its solution in chloroform dried. Concentration of the chloroform solution and dilution with methanol, followed by recrystallisations from the same solvent, yielded *12-oxo-oleana-9(11) : 18-dienyl acetate* (130 mg.) as plates, m. p. 268—269°, $[\alpha]_D$ +27° (*c*, 0·87) (Found: C, 79·7; H, 10·4. $C_{32}H_{48}O_3$ requires C, 79·95; H, 10·1%). Light absorption: Max. at 2500 Å ($\varepsilon = 10{,}900$); $\varepsilon_{2040} = 3900$. The methanol–chloroform mother-liquors gave a more soluble component identified as dioxo-β-amyradienyl acetate. Initial attempts to dehydrate the diol 3-monacetate by pyridine and phosphorus oxychloride (in air) were unsuccessful, oxidation intervening with the formation of dioxo-β-amyradienyl acetate.

12-Oxo-oleana-9(11) : 13(18)-dienyl Acetate from 12-Oxo-oleana-9(11) : 18-dienyl Acetate.—A solution of the 12-oxo-9(11) : 18-dienyl acetate (120 mg.) in acetic acid (25 c.c.) containing concentrated hydrochloric acid (3 c.c.) was heated on the steam-bath for 2 hr. The product was isolated by means of ether and treated with acetic anhydride (5 c.c.) and pyridine (10 c.c.) at room temperature overnight. 12-Oxo-oleana-9(11) : 13(18)-dienyl acetate (42 mg.) crystallised from methanol as prisms, m. p. 208—209°, $[\alpha]_D$ −81° (*c*, 1·15). Light absorption: Max. at 2060 ($\varepsilon = 9300$), 2640 ($\varepsilon = 9500$), and 2920 Å ($\varepsilon = 8600$). A mixture with the specimen described above was undepressed in m. p.

Hydrogenolysis of 12 : 19-Dioxo-olean-9(11)-enyl Acetate.—A solution of 12 : 19-dioxo-olean-9(11)-enyl acetate (537 mg.) in acetic acid (200 c.c.) was shaken with hydrogen and platinum (from 190 mg. of PtO_2). Absorption of hydrogen was slow and ceased after 21 hr. 19-Oxo-olean-9(11)-enyl acetate (413 mg.) crystallised from chloroform–methanol as plates, m. p. 256—258°, $[\alpha]_D$ +117°, +116° (*c*, 1·4, 0·8) (Found: C, 79·6; H, 10·4. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·4%). It gives a yellow colour with tetranitromethane and a mixture with the specimen described above was undepressed in m. p. Light absorption: $\varepsilon_{2060} = 2900$, $\varepsilon_{2100} = 2200$, $\varepsilon_{2150} = 1100$, $\varepsilon_{2200} = 280$.

Oxidation of 19-Oxo-olean-9(11)-enyl Acetate with Selenium Dioxide.—The acetate (83 mg.) in glacial acetic acid was refluxed with selenium dioxide (83 mg.) for 8 hr. The product was isolated by means of ether and treated with methanol. A relatively insoluble fraction (12 mg.), m. p. 283—286°, $[\alpha]_D$ +97° (*c*, 0·4), was not investigated further. The mother-liquor was evaporated to dryness and the residue crystallised from light petroleum from which dioxo-β-amyradienyl acetate (30 mg.) separated as prisms, m. p. 232—234°. Recrystallised from aqueous methanol, it separated as plates, m. p. and mixed m. p. 236—238°, $[\alpha]_D$ −91° (*c*, 0·5). Light absorption: Max. at 2780 Å ($\varepsilon = 11{,}000$).

12 : 19-Dioxo-18α-olean-9(11)-enyl Acetate.—A solution of 12 : 19-dioxo-olean-9(11)-enyl acetate (400 mg.) in 10% methanolic potassium hydroxide was refluxed for 3 hr. The product was acetylated (acetic anhydride–pyridine) and the acetate crystallised from methanol, to yield *12 : 19-dioxo-18α-olean-9(11)-enyl acetate* as plates, m. p. 279—281°, $[\alpha]_D$ +91°, +92°, +89·5° (*c*, 0·5, 1·2, 1·3) (Found: C, 77·6; H, 9·7. $C_{32}H_{48}O_4$ requires C, 77·4; H, 9·7%). Light absorption: Max. at 2430 Å ($\varepsilon = 11{,}700$).

19-*Oxo*-18α-*olean*-9(11)-*enyl Acetate*.—(*a*) A solution of 19-oxo-olean-9(11)-enyl acetate (1·3 g.) in 10% ethanolic potassium hydroxide (500 c.c.) was heated under reflux for 3 hr. The product was isolated by means of ether and acetylated (pyridine–acetic anhydride). Crystallisation from methanol–chloroform gave 19-*oxo*-18α-*olean*-9(11)-*enyl acetate* (1·14 g.) as blades or needles, m. p. 254—256°, $[\alpha]_D$ +139° (*c*, 1·2) (Found: C, 79·8; H, 10·4. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·4%).

(*b*) Catalytic hydrogenolysis of 12 : 19-dioxo-18α-olean-9(11)-enyl acetate was more difficult than that of the corresponding 18β-isomer. A solution of the 18α-diketone (1 g.) in glacial acetic acid (150 c.c.) was shaken with hydrogen and platinum (from 0·5 g. of PtO_2) for 48 hr. The filtered solution was added to freshly prepared platinum (from 0·25 g. of PtO_2) in glacial acetic acid (20 c.c.) and shaken with hydrogen for 24 hr. The product obtained by filtration and evaporation gave a pale yellow colour with tetranitromethane in chloroform and showed absorption maxima at 2070 (ε = 2100) and 2400 Å (ε = 3700). A solution of the product in light petroleum–benzene (2 : 1, 150 c.c.) was chromatographed on alumina (Grade II/III; 15 × 2 cm.). The same solvent mixture (250 c.c.) eluted a solid (260 mg.), crystallisation of which from chloroform–methanol yielded 19-oxo-18α-olean-9(11)-enyl acetate as blades, m. p. 257—259° [undepressed when mixed with the specimen described under (*a*)], $[\alpha]_D$ +136° (*c*, 1·2). Light absorption: $\varepsilon_{2080} = 3300$, $\varepsilon_{2100} = 2200$, $\varepsilon_{2150} = 670$. It gives a yellow colour with the tetranitromethane reagent. Continued washing of the alumina with the same solvent mixture (200 c.c.) gave intermediate fractions (total, 250 mg.) of 19-oxo-18α-olean-9(11)-enyl acetate of decreasing purity, whereafter benzene–ether (1 : 1; 100 c.c.) eluted a fraction (360 mg.), crystallisation of which from chloroform–methanol yielded 12 : 19-dioxo-18α-olean-9(11)-enyl acetate as plates, m. p. and mixed m. p. 282—284°, $[\alpha]_D$ +86° (*c*, 2·2) showing an absorption maximum at 2440 Å (ε = 9800).

Reduction of 19-*Oxo*-18α-*olean*-9(11)-*enyl Acetate with Lithium Aluminium Hydride*—A solution of 19-oxo-18α-olean-9(11)-enyl acetate (1·04 g.) in dry ether (100 c.c.) was treated with lithium aluminium hydride (0·5 g.) and refluxed for 1½ hr. The cold mixture was treated with water, and the product isolated in the usual manner. Crystallisation from methanol gave three crops, m. p.s 239—241°, 240—243°, and 240—244°, which were combined (0·89 g.) and recrystallised from the same solvent, to give 18α-*olean*-9(11)-*ene*-3 : 19β-*diol* as prismatic needles, m. p. 243—245°, $[\alpha]_D$ +108° (*c*, 1·1) (Found: C, 81·25; H, 11·5. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). Light absorption: $\varepsilon_{2080} = 2400$, $\varepsilon_{2150} = 940$, $\varepsilon_{2210} = 100$. The diol gives a pale yellow colour with tetranitromethane.

Treatment of the diol (0·81 g.) with acetic anhydride (10 c.c.) and pyridine (20 c.c.) at room temperature for 16 hr. followed by chromatography of a solution of the product (0·79 g.; m. p. 258—260°) in benzene on alumina gave 18α-*olean*-9(11)-*ene*-3 : 19β-*diol* 3-*acetate* (0·77 g.) which separates from chloroform–methanol as needles, m. p. 262—265°, $[\alpha]_D$ +112° (*c*, 1·1) (Found: C, 79·3; H, 10·8. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

Reduction of 19-*Oxo-olean*-9(11)-*enyl Acetate with Lithium Aluminium Hydride*.—The ketone (0·5 g.) in dry ether (200 c.c.) was treated with lithium aluminium hydride (0·5 g.) in ether (200 c.c.), and the mixture kept at room temperature for 4 hr. The product was isolated (mineral acid being avoided) and crystallised from aqueous methanol from which *olean*-9(11)-*ene*-3 : 19α-*diol* separated as prismatic needles or plates (according to the concentration), m. p. 204—205°, $[\alpha]_D$ +78°, +79° (*c*, 0·7, 1·3) (Found: C, 81·3; H, 11·5. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). Light absorption: $\varepsilon_{2100} = 2000$, $\varepsilon_{2150} = 1400$, $\varepsilon_{2200} = 470$. It gives a pale yellow colour with tetranitromethane.

Partial acetylation of the diol, with acetic anhydride and pyridine at room temperature as described for the isomeric 18α-diol, gave *olean*-9(11)-*ene*-3 : 19α-*diol* 3-*acetate*, prismatic needles (from chloroform–methanol), m. p. 262—263°, $[\alpha]_D$ +88°, +89° (*c*, 1·5, 0·9) (Found: C, 79·1; H, 10·9. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). Light absorption: $\varepsilon_{2090} = 2000$ $\varepsilon_{2150} = 820$, $\varepsilon_{2200} = 200$; it gives a pale yellow colour with tetranitromethane. A mixture of the monoacetate with the isomeric 18α-olean-9(11)-ene-3 : 19β-diol 3-acetate did not show a depression in m. p.

Olean-9(11)-ene-3 : 19α-diol 3-acetate (150 mg.) in glacial acetic acid (50 c.c.) was treated at room temperature with chromic anhydride (≡1·2O) in acetic acid (11·5 c.c.) added dropwise during 30 min., and the solution was kept at room temperature for 20 hr. 19-Oxo-olean-9(11)-enyl acetate was isolated in the usual manner and crystallised from chloroform–methanol as plates, m. p. and mixed m. p. 253—255°, $[\alpha]_D$ +118° (*c*, 0·8); a mixture with 19-oxo-18α-olean-9(11)-enyl acetate, m. p. 254—256°, $[\alpha]_D$ +139°, had m. p. 232—238°.

Oleana-9(11) · 18-*dienyl Acetate*.—(*a*) A solution of 18α-olean-9(11)-ene-3 : 19β-diol 3-acetate (280 mg.) in dry pyridine (30 c.c.) and phosphorus oxychloride (10 c.c.) was refluxed for 8 hr.

The product, isolated by the addition of water and filtration, was dried, and chromatographed in light petroleum (50 c.c.) on alumina. Light petroleum–benzene (20 : 1, 360 c.c.; then 1 : 1, 220 c.c.) eluted fractions (243 mg.; m. p.s between 251° and 258°) which were combined and crystallised from methanol–chloroform, to yield *oleana*-9(11) : 18-*dienyl acetate* as plates, m. p. 259—260°, $[\alpha]_D$ +101° (*c*, 1·1) (Found: C, 82·5; H, 10·9. $C_{32}H_{50}O_2$ requires C, 82·3; H, 10·8%). Light absorption: $\varepsilon_{2070} = 3500$, $\varepsilon_{2100} = 3100$, $\varepsilon_{2150} = 1000$, $\varepsilon_{2220} = 100$. It gives a yellow colour with tetranitromethane in chloroform.

(*b*) A solution of olean-9(11)-ene-3 : 19α-diol 3-acetate in pyridine (75 c.c.) and phosphorus oxychloride (25 c.c.) was heated on the steam-bath for 7 hr. The product, crystallised from chloroform–methanol, yielded oleana-9(11) : 18-dienyl acetate as plates, m. p. 256—257°, $[\alpha]_D$ +99° (*c*, 2·2) (Found: C, 82·6; H, 11·0%), undepressed in m. p. when mixed with the specimen described above.

(*c*) A solution of 12-oxo-oleana-9(11) : 18-dienyl acetate (44 mg.) in glacial acetic acid was shaken with a platinum catalyst (from 100 mg. of PtO_2) and hydrogen for 18 hr. Isolation in the usual manner and two crystallisations from chloroform–methanol yielded oleana-9(11) : 18-dienyl acetate (21 mg.), plates, m. p. 257—258°, $[\alpha]_D$ +99° (*c*, 0·9). Light absorption: $\varepsilon_{2060} = 3300$. The m. p. of a mixture with a specimen prepared by method (*a*) was not depressed.

Hydrolysis of oleana-9(11) : 18-dienyl acetate using lithium aluminium hydride gave *oleana*-9(11) : 18-*dienol* which separated from *n*-hexane as fine matted needles, m. p. 158—159°, $[\alpha]_D$ +87° (*c*, 1·2) (Found: C, 84·5; H, 11·5. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). Light absorption: $\varepsilon_{2070} = 4100$, $\varepsilon_{2100} = 3450$, $\varepsilon_{2200} = 280$. Acetylation as above gave the acetate, plates (from chloroform–methanol), m. p. 257—258°, $[\alpha]_D$ +100° (*c*, 1·5).

Conversion of Oleana-9(11) : 18-*dienyl Acetate into Oleana*-11 : 13(18)-*dienyl Acetate*.—A solution of oleana-9(11) : 18-dienyl acetate (208 mg.) in acetic acid (100 c.c.) and concentrated hydrochloric acid (3 c.c.) was heated on a steam-bath for 20 hr. The product, after treatment with acetic anhydride and pyridine, was crystallised from methanol–chloroform to yield oleana-11 : 13(18)-dienyl acetate as plates, m. p. 228—229° (undepressed when mixed with an authentic specimen, m. p. 227—228°), $[\alpha]_D$ −63° (*c*, 1·2). Light absorption: Max. at 2420 (ε = 27,500), 2510 (ε = 31,000) and 2600 Å (ε = 20,100).

Oxidation of 18α-*Olean*-9(11)-*ene*-3 : 19β-*diol* 3-*Acetate with Hydrogen Peroxide*.—A refluxing solution of this acetate (2·9 g.) in glacial acetic acid (400 c.c.) was treated during 10 min. with hydrogen peroxide (100-vol; 30 c.c.) in acetic acid (30 c.c.), then refluxed for 1 hr. and again treated during 10 min. with hydrogen peroxide (100-vol.; 20 c.c.) in acetic acid (20 c.c.), whereafter the mixture was refluxed for 2 hr. The hot solution was treated with water until a crystalline solid (1·4 g.; m. p. 318—327°) separated. After cooling, the solid was collected and crystallised from methanol–chloroform, to yield 11-*oxo*-18α-*oleanane*-3 : 19β-*diol* 3-*acetate* (1·1 g.) as prismatic needles, m. p. 334—336°, $[\alpha]_D$ +36° (*c*, 1·3) (Found: C, 77·1; H, 10·6. $C_{32}H_{52}O_4$ requires C, 76·75; H, 10·5%).

18α-*Oleanane*-3 : 19β-*diol* 3-*Acetate*.—A mixture of 11-oxo-18α-oleanane-3 : 19β-diol 3-acetate (0·7 g.), methanolic sodium methoxide (from 1·75 g. of sodium and 22 c.c. of methanol), and hydrazine hydrate (100%; 7 ml.) was heated at 200—210° for 19 hr. A portion of the product (90 mg.), isolated in the usual manner, was crystallised from aqueous methanol, to yield 18α-oleanane-3 : 19β-diol as prismatic needles, m. p. 267—268°, $[\alpha]_D$ +26° (*c*, 0·7), undepressed in m. p. when mixed with a specimen, m. p. 265·6—267°, prepared from lupeol. The remainder of the product was kept with acetic anhydride–pyridine at room temperature overnight. The acetylated product (560 mg.) was purified by chromatography on alumina, to yield 18α-oleanane-3 : 19β-diol 3-monoacetate as long blades, m. p. 289—293°, $[\alpha]_D$ +35° (*c*, 0·7). Ames *et al.* (*loc. cit.*) give m. p. 294·5—295°, $[\alpha]_D$ +33°. Dehydration of the monoacetate as described by Ames *et al.* yielded germanicyl acetate, plates (from chloroform–methanol), m. p. 277—279°, $[\alpha]_D$ +17° (*c*, 0·8). Simpson (*J.*, 1944, 283) gives m. p. 274°, $[\alpha]_D$ +18°. Alkaline hydrolysis yielded germanicol, needles (from methanol), m. p. 178—180°, $[\alpha]_D$ +5° (*c*, 0·6). Simpson (*loc. cit.*) gave m. p. 176—177°, $[\alpha]_D$ +6°.

We are glad to express our indebtedness to Mr. J. Adam for the preparation of intermediates and to Dr. A. C. Syme and Mr. Wm. McCorkindale for the micro-analyses and ultra-violet absorption spectra. Two of us (J. D. J. and L. C. McK.) thank the Department of Scientific and Industrial Research for Maintenance Awards.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, May 26th*, 1953.]

738. *Triterpene Resinols and Related Acids. Part XXVIII.* The Non-saponifiable Fraction from* Strychnos nux-vomica *Seed Fat: The Structure of* cyclo*Artenol.*

By H. R. Bentley, J. A. Henry, D. S. Irvine, and F. S. Spring.

The non-saponifiable fraction from the seed fat of *Strychnos nux-vomica L.* contains α-amyrin, *cyclo*artenol, and stigmasterol. *cyclo*Artenol is shown to be a *cyclo*lanost-24-enol containing a *cyclo*propane bridge extending from $C_{(9)}$ (cf. *Chem. and Ind.*, 1953, 217).

After preliminary work by Schröder (*Arch. Pharm.*, 1905, **243**, 633), the non-saponifiable fraction of *Strychnos nux-vomica* seed fat was investigated in some detail by Heiduschka and Wallenreuter (*ibid.*, 1912, **250**, 398; 1915, **253**, 202) who isolated three crystalline alcohols. One of these, m. p. 158°, was described as a phytosterol, analysis of which corresponded to the formula $C_{27}H_{46}O,H_2O$; a second alcohol, m. p. 115°, was formulated as $C_{32}H_{54}O$, and a third, m. p. 186°, as $C_{35}H_{58-60}O$. Several esters of the alcohol, m. p. 186°, were prepared and it was observed that oxidation of the acetate, m. p. 223°, with chromic oxide gave a product resembling "oxy-amyrin acetate." Through the courtesy of the Directors of Messrs. T. & H. Smith, Limited, Edinburgh, we have re-examined *S. nux-vomica* seed fat and have isolated and identified these three alcohols.

The fat contains a high proportion (12—15%) of non-saponifiable matter. Acetylation and chromatography of this gave four well-defined fractions. The first, a colourless volatile oil, has not been examined in detail. Purification of the second readily gave α-amyrin acetate, characterised by hydrolysis to α-amyrin, m. p. 185°. Purification of the final fraction gave an acetate, m. p. 142·5—143°, which after hydrolysis gave stigmasterol, m. p. 165·5—167·5°. The third fraction readily gave an acetate, m. p. 122—124°, hydrolysis of which yielded *cyclo*artenol, $C_{30}H_{50}O$, m. p. 99°, raised to 115° after rigorous drying. This identification follows from a comparison of the constants of the alcohol and its derivatives with those of corresponding derivatives described by Barton (*J.*, 1951, 1444); the identities of the alcohol and its acetate have been confirmed by mixed m. p. determinations kindly made by Dr. D. H. R. Barton.

	From *S. nux-vomica*		From *A. integrifolia*		
	M. p.	$[\alpha]_D$	M. p.	$[\alpha]_D$	Mixed m. p.
*cyclo*Artenol	115° (99° solvated)	+54°	85—92°	+48°	112—113·5° (sinters 110°)
Acetate	122—124	+59·5	122·5—123·5	+58	121·5—122·5
Benzoate	130	+76	129—130	+65	—
*cyclo*Artenone	105—106	+22	109	+24	—
*cyclo*Artanol	99	+50	99—101	+45	—
Acetate	130—132	+59	132—133	+45	—

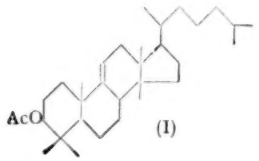
Barton isolated *cyclo*artenol together with the corresponding ketone *cyclo*artenone, $C_{30}H_{48}O$, from the latex of the fruit of *Artocarpus integrifolia*. *cyclo*Artenol has since been recognised as a minor constituent of the latex of *Euphorbia balsamifera* (Chapon and David, *Bull. Soc. chim.*, 1952, 456) and is probably identical with handianol from *Euphorbia handiensis* (Gonzalez, Calero, and Calero, *Anal. Fis. Quím.*, 1949, **45**, *B*, 1441; Gonzalez and Calero, *ibid.*, **46**, *B*, 175).

The presence of an *iso*propylidene group in a side chain, and of a *cyclo*propane ring, in *cyclo*artenol has been established by Barton (*loc. cit.*). These observations have been confirmed and extended by us. Ozonolysis of *cyclo*artenyl acetate yields acetone and oxidation with chromic acid in acetic acid gives an acid, $C_{29}H_{46}O_4$ (trisnor*cyclo*artanoloic acid acetate), characterised as its methyl ester.

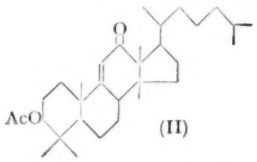
Hydrogenation of *cyclo*artenyl acetate readily gave *cyclo*artanyl acetate, treatment of which with hydrogen chloride in chloroform gives a mixture, m. p. 137—157°, $[\alpha]_D$ +68°.

* Part XXVII, preceding paper.

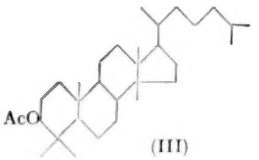
In contrast to the parent *cyclo*artanyl acetate, this mixture gave a strong yellow colour with tetranitromethane and showed selective absorption between 1950 and 2200 Å characteristic of unsaturation. Attempted purification of the mixture by crystallisation and chromatography, and by chromatography of the derived benzoate, alcohol, and ketone mixtures failed to give a homogeneous product. A homogeneous component was isolated from the acetate mixture by treatment with chromic acid in acetic acid (cf. Marker, Wittle, and Mixon, *J. Amer. Chem. Soc.*, **1937**, **59**, 1368). The component which escaped oxidation was readily separated and proved to be lanost-9(11)-enyl acetate (I) (Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893; McGhie,



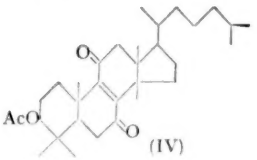
(I)



(II)



(III)



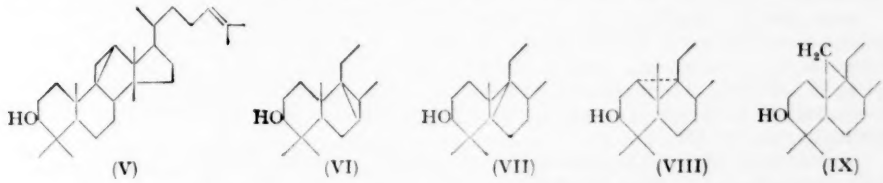
(IV)

Pradhan, and Cavalla, *J.*, 1952, 3176). The artenyl acetate described by Barton is probably largely lanost-9(11)-enyl acetate. 7 : 11-Dioxolanost-8-enyl acetate was not isolated from the oxidation mixture; chromatography gave small fractions which, although they could not be adequately purified, showed the characteristic ultra-violet absorption spectrum of 7 : 11-dioxolanost-8-enyl acetate.

Hydrogenation of the hydrogen chloride isomerisation product from *cyclo*artanyl acetate under conditions known to ensure complete hydrogenation of lanost-9(11)-enyl acetate (Voser *et al.*, *loc. cit.*) yielded a product which still gives a yellow colour with tetranitromethane and shows selective absorption at 2070 Å. Treatment of this mixture with chromic acid followed by chromatography gave lanostanyl acetate (III) in 50—60% yield together with 10% of 7 : 11-dioxolanost-8-enyl acetate (IV). The last compound is formed by the oxidation of lanost-8-enyl acetate (XI) or lanost-7-enyl acetate (XII) with chromic acid (Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472; Dorée and McGhie, *Nature*, 1944, **153**, 148; Voser *et al.*, *loc. cit.*; Cavalla, McGhie, and Pradhan, *J.*, 1951, 3142), but not by oxidation of lanost-9(11)-enyl acetate with chromic acid. The last reaction yields 12-oxolanost-9(11)-enyl acetate (II) which is also obtained by relatively vigorous oxidation of the acetate mixture, m. p. 137—157°, with the same reagent. These results imply that the acetate mixture contains a relatively large proportion of lanost-9(11)-enyl acetate and a smaller quantity of lanost-7- and/or -8-enyl acetate.

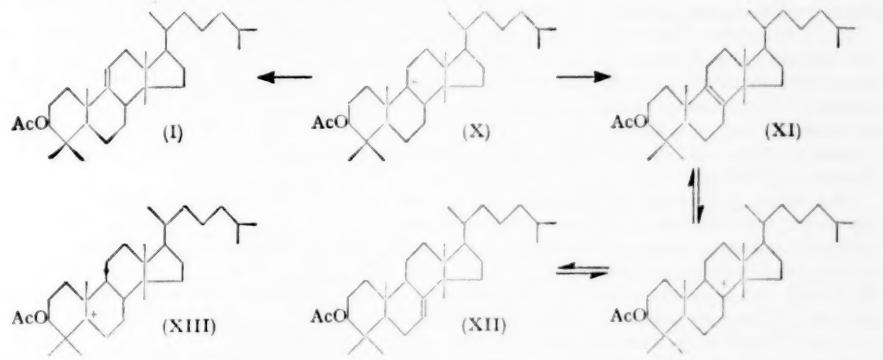
Lanost-9(11)-enyl acetate is recovered unchanged in quantitative yield after treatment with hydrogen chloride in chloroform and it is not obtained by similar treatment of lanost-8- or -7-enyl acetate. Similar treatment of lanost-8-enyl acetate gives a mixture from which lanost-7-enyl acetate has been isolated (Marker, Wittle, and Mixon, *loc. cit.*; Cavalla, McGhie, and Pradhan, *loc. cit.*; Barton, Fawcett, and Thomas, *J.*, 1951, 3147). The initial product obtained from the last reaction is probably an equilibrium mixture of the 7- and 8-enyl acetates; it does not contain any appreciable amount of the 9(11)-isomer since oxidation of the equilibrium mixture with chromic anhydride gives 7 : 11-dioxolanost-8-enyl acetate in high yield, and chromatography of the product failed to disclose the presence of 12-oxolanost-9(11)-enyl acetate. Although we have only accounted for approximately 60—70% of the acetate mixture, m. p. 137—157°, as lanost-9(11)-enyl acetate (50—60%) and lanost-7- and -8-enyl acetate (approx. 10%) we believe that the mixture contains only these three components. Crystallisation of a mixture of lanost-9(11)enyl acetate (60%)

and the equilibrium mixture of lanost-7- and -8-enyl acetates (40%) gave an acetate mixture which closely resembled the acetate mixture, m. p. 137—157°.



(V) (VI) (VII) (VIII) (IX)

The simplest explanation of the formation of lanost-9(11)-enyl acetate in high yield by the action of mineral acid on *cyclo*artanyl acetate is that the *cyclo*propane ring in *cyclo*artenol extends from $C_{(9)}$. The evidence at present available does not allow a satisfactory choice to be made from the structures (V)—(IX) for *cyclo*artenol, the acetyl dihydro-derivative from each of which may yield with mineral acid the carbonium intermediate (X), the subsequent fate of which is depicted below:



Structure (VII) appears improbable since the mixed acetates, m. p. 137—157°, do not contain any appreciable quantity of rearrangement products derived from the carbonium ion (XIII).

Experimental

Rotations were measured in chloroform solution at approx. 15°, and ultra-violet absorption spectra were measured in ethanol solutions using a Unicam SP. 500 spectrophotometer. Grade II alumina and a light petroleum fraction of b. p. 60—80° were used for chromatography unless otherwise specified.

α-Amyrin Acetate.—A solution of sodium hydroxide (160 g.) in water (200 ml.) was added to one of *S. nux-vomica* fat (1 kg.) in ethanol (3 l.), and the mixture was boiled under reflux for 4 hr., concentrated, and mixed with hot water (12 l.). The dry non-saponifiable matter (125 g.), isolated by means of ether, in acetic anhydride (100 ml.) and dry pyridine (250 ml.) was kept for 24 hr. at room temperature and the product isolated by means of ether. The acetylated product formed an orange-coloured waxy solid (130 g.). A solution of the solid in light petroleum (1 l.) was percolated through a column (132 × 5·5 cm.) of alumina (3 kg.), and the chromatogram eluted with (*a*) light petroleum (5 l.), (*b*) light petroleum–benzene (1 : 1; 7 l.), (*c*) benzene (2 l.), (*d*) benzene–ether (9 : 1; 5 l.), and (*e*) acetone (6 l.). Evaporation of fraction (*a*) gave a colourless oil (6·5 g.) which has not been examined. Fraction (*b*) gave a solid (44·0 g.) which, after crystallisation from chloroform–methanol, yielded α-amyrin acetate as plates, m. p. and mixed m. p. 223—225°, $[\alpha]_D$ +79·5° (*c*, 1·6) (Found: C, 81·8; H, 11·2. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). Alkaline hydrolysis of the acetate yielded α-amyrin which separated from aqueous methanol as needles, m. p. and mixed m. p. 185°, $[\alpha]_D$ +82° (*c*, 2·0). Fraction (*c*) gave a clear gum (3·5 g.) which was not examined.

cyclo*Artenyl Acetate.*—Fraction (*d*) (above) gave a crystalline solid (26·4 g.), repeated

crystallisation of which from chloroform–methanol gave *cyclo*artenyl acetate (12·1 g.) as plates (Found: C, 81·9; H, 11·4. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). For this and other *cyclo*artenol derivatives see also the Table (p.).

cyclo*Artenol*.—Hydrolysis of the acetate with methanolic potassium hydroxide gave *cyclo*artenol which separated from methanol as needles, m. p. 99° raised to 115° after drying for 12 hr. at 65° *in vacuo*, $[\alpha]_D$ +54° (c, 1·25) (Found: C, 84·5; H, 11·8. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%). The formation of solvated crystals by crystallisation of *cyclo*artenol from methanol is a characteristic property. On drying in high vacuum at 65° the m. p. of the crystals gradually rises to 115°.

*cyclo*Artenyl benzoate separated from methanol as needles (Found: C, 83·5; H, 10·25. Calc. for $C_{37}H_{54}O_2$: C, 83·7; H, 10·25%).

cyclo*Artenone*.—Oxidation of *cyclo*artenol (600 mg.) with chromic acid (104 mg.) in acetic acid (60 ml.) for 12 hr. at room temperature and isolation of the product in the usual way gave *cyclo*artenone, plates from methanol (Found: C, 85·0; H, 11·35. Calc. for $C_{30}H_{48}O$: C, 84·8; H, 11·4%).

cyclo*Artanyl Acetate*.—Hydrogenation of *cyclo*artenyl acetate in presence of a platinum catalyst in acetic acid gave *cyclo*artanyl acetate, needles from methanol–chloroform (Found: C, 81·8; H, 11·8. Calc. for $C_{32}H_{54}O_2$: C, 81·6; H, 11·6%), hydrolysed by alkali to *cyclo*artanol, plates from methanol (Found: C, 84·1; H, 12·3. Calc. for $C_{30}H_{52}O$: C, 84·0; H, 12·2%).

cyclo*Artanone*.—A solution of chromic acid (125 mg.) in acetic acid (10 ml.) was added dropwise with stirring during 1 hr. to a solution of *cyclo*artanol (660 mg.) in acetic acid (70 ml.). After 16 hr. methanol (5·0 ml.) was added, the solution was diluted with water (500 ml.), and the neutral product isolated in the usual manner. Crystallisation of this from methanol gave cyclo*artanone* (510 mg.) as plates, m. p. 110°, $[\alpha]_D$ +24° (*c*, 2·9) (Found: C, 84·4; H, 11·9. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). The *semicarbazone* formed needles, m. p. 215°, from methanol (Found: C, 76·9; H, 10·6. $C_{31}H_{53}ON_3$ requires C, 77·0; H, 11·0%)].

Ozonolysis of cyclo*Artenyl Acetate*.—An ice-cold solution of *cyclo*artenyl acetate (2·0 g.) in dry carbon tetrachloride (50 ml.) was treated with ozonised oxygen (5—7%) until a sample of the solution no longer absorbed bromine (4 hr.). The residue obtained after evaporation was decomposed by boiling it under reflux for 40 min. with water (250 ml.). The mixture was distilled and the distillate (100 c.c.) treated with 2:4-dinitrophenylhydrazine in hydrochloric acid, which gave acetone 2:4-dinitrophenylhydrazone (120 mg.), yellow needles (from ethanol), m. p. and mixed m. p. 128° (Found: N, 23·4. Calc. for $C_9H_{10}O_4N_4$: N, 23·5%). Extraction of the non-volatile solid with ether, separation into acidic and neutral fractions, and attempted chromatographic purification of these did not yield homogeneous products.

*Trisnor*cyclo*artanoloic Acid*.—Chromic acid (2·8 g.) in water (3 ml.) and acetic acid (85 ml.) was added dropwise during 90 min. to a boiling solution of *cyclo*artenyl acetate (2·0 g.) in acetic acid (100 ml.). The mixture was evaporated and the dry residue shaken with sulphuric acid (2%; 250 ml.) and ether. The ethereal solution was washed with water (100 ml.) and with sodium hydroxide solution (3%; 3 × 100 ml.); a sodium salt separated at the solvent interface. The salt was collected and suspended in water (100 ml.), the mixture acidified (methyl-red) with hydrochloric acid, and the solid collected by means of ether. *Trisnor*cyclo*artanoloic acid acetate* (104 mg.) separated from aqueous acetone as short prismatic needles, m. p. 221·5—223°, $[\alpha]_D$ +62° (*c*, 0·9) (Found: C, 76·2; H, 10·3. $C_{29}H_{46}O_4$ requires C, 75·95; H, 10·1%). With ethereal diazomethane this gave the *methyl ester acetate*, needles, m. p. 121—123° (from methanol) $[\alpha]_D$ +56° (*c*, 1·6) (Found: C, 76·0; H, 10·2. $C_{30}H_{48}O_4$ requires C, 76·2; H, 10·2%). Neither the alkali-soluble acidic nor the neutral fraction obtained from the oxidation mixture yielded homogeneous products.

Isomerisation of cyclo*Artanyl Acetate*.—Treatment of *cyclo*artanyl acetate with hydrogen chloride in chloroform as described by Barton (*loc. cit.*) gave a product which crystallised from methanol–chloroform as plates, m. p. 137—157°, $[\alpha]_D$ +68° (*c*, 2·4). Light absorption: Max. at 2070 Å (ε = 3600). Repeated crystallisation from the same solvent was accompanied by a gradual and continuous increase in m. p. and considerable loss of material. After five recrystallisations, the product had m. p. 157—159°, $[\alpha]_D$ +76° (*c*, 1·7). Alkaline hydrolysis of the acetate mixture, m. p. 137—157°, gave an alcohol mixture, m. p. 152—154°, $[\alpha]_D$ +60° (*c*, 1·5) (benzoate, m. p. 197—198°), acetylation of which gave an acetate, m. p. 137—160°. These observations confirm those of Barton (*loc. cit.*) who also noted the sharp m. p. of the alcohol and benzoate mixtures. The equilibrium mixture of lanost-7- and -8-enyl acetates (40 mg.) (Cavalla, McGhie, and Pradhan, *loc. cit.*) was mixed with lanost-9(11)-enyl acetate (60 mg.) and crystallised from methanol–chloroform, in plates, m. p. 138—158°, $[\alpha]_D$ +73° (*c*, 2·1), which

melted over the same range when mixed with a sample of the acetate, m. p. 137—157°. Hydrolysis gave an alcohol mixture, $[\alpha]_D$ +63° (*c*, 1·8), m. p. 153—154° alone or mixed with a specimen of the alcohol, m. p. 152—154°.

Lanost-9(11)-enyl Acetate.—Chromic acid (0·3 g.) in 90% acetic acid (25 ml.) was added during 5 min. with stirring to a solution of the acetate mixture (m. p. 137—157°; 1·0 g.) in acetic acid (75 ml.) heated on the steam-bath. Heating was continued for 10 min., the mixture was poured into water (500 ml.), and the solid collected by means of ether. A solution of the dry solid (1·1 g.) in light petroleum (100 ml.) was filtered through a column (23 × 2 cm.) containing alumina (60 g.), and the chromatogram developed by elution with light petroleum and light petroleum–benzene (9 : 1; then 4 : 1). The last solvent eluted a fraction (m. p. 167—170°; 448 mg.) which on crystallisation from chloroform–methanol gave lanost-9(11)-enyl acetate as hexagonal plates, m. p. 170—172°, $[\alpha]_D$ +85° (*c*, 1·63) (Found: C, 81·5; H, 11·8. Calc. for $C_{32}H_{54}O_2$: C, 81·6; H, 11·6%). When mixed with a specimen (m. p. 173°, $[\alpha]_D$ +84°) prepared from lanost-8-enyl acetate (Voser *et al.*, and McGhie, Pradhan, and Cavalla, *loc. cit.*) the m. p. was undepressed. Lanost-9(11)-enyl acetate was recovered in high yield after treatment with dry hyrogen chloride in chloroform for 3 hr.

Lanost-9(11)-enol.—A solution of lanost-9(11)-enyl acetate (0·2 g.) in ethanolic potassium hydroxide (3%; 25 ml.) was heated under reflux for 3 hr. The product, isolated by means of ether and crystallised from methanol, gave *lanost-9(11)-enol* (0·16 g.) as matted needles, m. p. 167°, $[\alpha]_D$ +76° (*c*, 0·84) (Found: C, 83·8; H, 12·4. $C_{30}H_{52}O$ requires C, 84·0; H, 12·2%).

12-Oxolanost-9(11)-enyl Acetate.—Chromic acid (0·22 g.) in acetic acid (50 ml.) was added during 1 hr. to a refluxing solution of lanost-9(11)-enyl acetate (0·5 g.) in acetic acid (50 ml.). The solution was heated under reflux for 2 hr., kept overnight at room temperature, and mixed with water (300 ml.), and the solid collected by means of ether. A solution of the yellow crystalline product (0·53 g.) in light petroleum (100 ml.) was filtered through a column (1·5 × 13 cm.) of alumina (20 g.), and the chromatogram eluted with light petroleum, light petroleum–benzene (4 : 1), benzene, and benzene–ether (9 : 1). The fraction (0·16 g.) eluted by light petroleum–benzene was lanost-9(11)-enyl acetate, m. p. 170—171°, $[\alpha]_D$ +84° (*c*, 1·5). The fractions eluted with benzene and benzene–ether (0·2 g.) were combined and crystallised from methanol, to yield *12-oxolanost-9(11)-enyl acetate* as needles, m. p. 184—185°, $[\alpha]_D$ +91° (*c*, 0·62) (Found: C, 78·3; H, 10·9. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). Light absorption in ethanol: Max. at 2420 Å (ε = 9800). The αβ-unsaturated ketone was also obtained (in low yield) by vigorous oxidation of the mixed acetates, m. p. 137—157°, with chromic acid.

Lanostanyl Acetate.—(*a*) A solution of the acetate mixture, m. p. 137—157° (0·84 g.), in acetic acid (150 ml.) was shaken with hydrogen and platinum (500 mg.) for 24 hr. at 80°. The solution was filtered and evaporated, to give a crystalline solid (0·84 g.) which gave a yellow colour with tetranitromethane and showed light absorption at 2070 Å (ε = 2600). Chromic acid (0·32 g.) in acetic acid (25 ml.) was added during 30 min. with stirring to a solution of the hydrogenation product (0·84 g.) in acetic acid (100 ml.) heated on the steam-bath, and heating was continued for 90 min. The cooled solution was mixed with methanol (25 ml.) and evaporated to dryness, and the residue diluted with water (200 ml.). The neutral product (0·82 g.), isolated by means of ether, in light petroleum (50 ml.) was filtered through a column (2 × 12 cm.) of alumina (25 g.). Elution with light petroleum–benzene (4 : 1; 375 ml.) gave a solid (0·48 g.) which on crystallisation from chloroform–methanol gave lanostanyl acetate as needles, m. p. 155—156°, $[\alpha]_D$ +41° (*c*, 1·6) (Found: C, 81·3; H, 12·0. Calc. for $C_{32}H_{56}O_2$: C, 81·3; H, 11·9%), identified by direct comparison with an authentic specimen, m. p. 155—156°, $[\alpha]_D$ +41° (*c*, 1·16), prepared as described by Voser *et al.* (*loc. cit.*). Elution with light petroleum–benzene (1 : 4; 100 ml.) and with benzene (150 ml.) gave a partly crystalline product (83 mg.) which on crystallisation from methanol gave 7 : 11-dioxolanost-8-enyl acetate as pale yellow plates, m. p. and mixed m. p. 155—156°, $[\alpha]_D$ +91° (*c*, 0·57) (Found: C, 77·2; H, 10·4. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1%). Light absorption in ethanol: Max. at 2060 (ε = 3800) and 2700 Å (ε = 7600).

(*b*) A solution of 12-oxolanost-9(11)-enyl acetate (100 mg.) in acetic acid (100 ml.) was shaken with hydrogen and platinum catalyst (200 mg.) for 24 hr. at 80°. The filtered solution was evaporated and the residue dissolved in light petroleum (b. p. 40—60°; 40 ml.) and purified by absorption on alumina (10 g.) and elution with light petroleum–benzene (7 : 3) which gave lanostanyl acetate (80 mg.) as needles (from chloroform–methanol), m. p. and mixed m. p. 156°, $[\alpha]_D$ +40·5° (*c*, 0·67) (Found: C, 81·51; H, 12·05%).

9 : 11-*Epoxylanostanyl Acetate.*—A mixture of lanost-9(11)-enyl acetate (100 mg.) and perhydrol (0·5 ml.) in acetic acid (100 ml.) was heated on the steam-bath for 2 hr. The cooled solution was diluted with water, and the crystalline product collected, washed with water,

dried, and recrystallised from methanol, giving 9 : 11-*epoxylanostanyl acetate* (60 mg.) as plates, m. p. 181—182°, $[\alpha]_D$ +29° (*c*, 0·73) (Found: C, 79·2; H, 11·4. $C_{32}H_{54}O_3$ requires C, 79·0; H, 11·2%). The compound gives no colour with tetranitromethane and shows no selective light absorption in the ultra-violet region; it is probably identical with the "artenyl acetate oxide" described by Barton (*loc. cit.*).

Wolff–Kishner Reduction of 7 : 11-*Dioxolanostanyl Acetate.*—By using the Huang-Minlon modification described by McGhie, Pradhan, and Cavalla (*loc. cit.*) 7 : 11-dioxolanostanyl acetate readily gave 11-oxolanostanyl acetate, m. p. 143—144°, $[\alpha]_D$ +64° (*c*, 1·07). When the normal Wolff–Kishner method was used, however, the reduction proceeded in a different direction.

A mixture of 7 : 11-dioxolanostanyl acetate (5·0 g.) and hydrazine hydrate (100%; 11·0 ml.) in dry ethanol (130 ml.) was boiled under reflux for 2 hr., a solution of sodium (12·0 g.) in ethanol (150 ml.) was added and the mixture heated at 200° in an autoclave for 16 hr. The cooled mixture was diluted with water (1 l.), and the product (4·9 g.) collected by means of ether and acetylated on the steam-bath for 45 min. with acetic anhydride (20 ml.) and pyridine (30 ml.). A solution of the acetylated product (5·1 g.) in light petroleum (b. p. 40—60°)–benzene (4 : 1) was filtered through a column (3·8 × 24 cm.) of alumina (210 g.). The combined, partly crystalline fractions (4·1 g.) eluted by light petroleum–benzene (1 : 4), benzene, and benzene–ether (9 : 1), when recrystallised from methanol, yielded 3 : 7-diacetoxylanostan-11-ol as fine needles, m. p. 236—237°, $[\alpha]_D$ +58° (*c*, 1·0) (Found: C, 74·8; H, 10·8. Calc. for $C_{34}H_{58}O_5$: C, 74·7; H, 10·7%). A specimen prepared by the method of Voser *et al.* (*loc. cit.*) had m. p. and mixed m. p. 236—237°, $[\alpha]_D$ +57° (*c*, 0·95) (Voser *et al.* give m. p. 235—236°, $[\alpha]_D$ +73°).

Stigmasterol (with M. B. E. Fayez).—Evaporation of fraction (*e*) from the original chromatogram gave a brown resin (25 g.) which was combined with similar fractions from three experiments. Acetylation of the resin (*ca.* 100 g.) with pyridine and acetic anhydride yielded a resinous acetate (108 g.). A solution of this in light petroleum (b. p. 40—60°) was filtered through a column (5·5 × 120 cm.) of alumina (4000 g.). Crystallisation of a series of fractions eluted by light petroleum–benzene (1 : 1) gave (in decreasing ease of elution), α-amyrin acetate (40 g.), m. p. and mixed m. p. 223°, *cyclo*artenyl acetate (15 g.), m. p. and mixed m. p. 122°, and a steroid acetate (*ca.* 5 g.), m. p. 135°. Repeated recrystallisation from chloroform–methanol of the steroid fractions, which gave a green Liebermann–Burchard reaction, yielded stigmasteryl acetate (1·5 g.) as flat needles, m. p. 142·5—143°, $[\alpha]_D$ −51° (Found: C, 81·9; H, 11·1. Calc. for $C_{31}H_{50}O_2$: C, 81·9; H, 11·1%), identified by comparison with an authentic specimen, m. p. 142—143°, $[\alpha]_D$ −51°, kindly supplied by Dr. D. H. R. Barton. Hydrolysis gave stigmasterol as needles (from chloroform–methanol), m. p. 165·5—167·5°, $[\alpha]_D$ −49° (Found: C, 83·8; H, 11·9. Calc. for $C_{29}H_{48}O$: C, 84·5; H, 11·7%), and bromination in ether–acetic acid gave stigmasteryl acetate tetrabromide which forms small needles, m. p. 203°, $[\alpha]_D$ −39°, from ethanol–chloroform (Found: C, 48·1; H, 6·6; Br, 40·6. Calc. for $C_{31}H_{50}O_2Br_4$: C, 48·1; H, 6·5; Br, 41·3%).

We are glad to acknowledge our indebtedness to the Directors of Messrs. T. & H. Smith, Ltd., Edinburgh, who supplied us with the fat and later the non-saponifiable matter from *S. nux-vomica*, to Dr. C. L. Hewitt of Organon Laboratories Ltd., Newhouse, Lanarkshire, who supplied us with lanostadienyl acetate, and to Mr. M. B. E. Fayez, B.Sc., who examined and identified the sterol fraction. One of us (J. A. H.) thanks the Governors of The Royal Technical College for the award of the Crawford and Duncan Scholarships, and another (D. S. I.) expresses his thanks to the Department of Scientific and Industrial Research for a Maintenance Award.

The Royal Technical College, Glasgow. [*Received, June 26th,* 1953.]

739. *Adaptation of* Bact. lactis aerogenes *to resist Phenol and Various Alkylphenols.*

By L. S. Phillips and Sir Cyril Hinshelwood.

Two types of phenomenon are observed in the adaptation of *Bact. lactis aerogenes* serially subcultured in the presence of sub-lethal concentrations of alkylphenols in a synthetic medium. The first, a very slow and difficult increase of growth rate, is exemplified by growth in phenol itself. The second, a rapid elimination, after one or two subcultures, of an initial very long lag (not shown with phenol) is exemplified by growth in thymol (which acts at much lower concentrations than phenol). Behaviour intermediate between the two extreme types is also observed, and it is concluded that for the whole series of alkylphenols there exists a gradual transition from the one to the other.

The thymol type of behaviour is shown with phenols containing branched side-chains which are thought to exert specific effects of their own superposed on the general phenolic action.

Bact. lactis aerogenes (*Aerobacter aerogenes*) can be trained by serial transfer in presence of sub-inhibitory concentrations of many toxic substances to show a high degree of resistance to their action. Although there are statements in the literature about coliform strains resistant to phenols (Meader and Fairer, *J. Infect. Dis.*, 1926, **39**, 237), all attempts in this laboratory to produce phenol-resistant varieties of the strain currently in use have hitherto yielded negative results. The normal generation time in a glucose–ammonium sulphate synthetic medium is about 30 minutes, and after 100 subcultures (about 1000 generations) at a phenol concentration giving a generation time of 50 minutes (D. S. Davies, unpublished observations) there was no detectable improvement in growth rate. On the other hand, training to thymol occurred readily (Dean and Hinshelwood, *Proc. Roy. Soc.*, 1952, *B*, **140**, 339).

The object of the present work was to obtain more systematic information about the behaviour of the bacterium with various substituted phenols. The question of the mechanism of the training process itself (mutation–selection or general adaptive response) will not be treated, the primary consideration being the influence of chemical structure on contrasting types of behaviour.

Organism, Methods, and Media.—The organism was a strain of *Bact. lactis aerogenes* obtained originally from the National Collection of Type Cultures and maintained in the laboratory for the last ten years. When used it was thoroughly equilibrated with a synthetic medium prescribed by Gladstone, Fildes, and Richardson (*Brit. J. Exp. Path.*, 1935, **16**, 335) and consisting of glucose, ammonium sulphate, magnesium sulphate, with sodium and potassium phosphates. The pH was 7·1. In this medium at 40·0° and with a stream of sterilised air the mean generation time was 29 minutes and the lag of an inoculum transferred in the logarithmic phase was zero.

Growth rates were measured turbidimetrically with a photoelectric turbidimeter. Mean generation times (m.g.t.) were obtained from logarithmic plots and lags by extrapolation of the logarithmic line to the measured inoculum size.

After serial subculture in presence of drugs the resulting strains were finally tested by Gram-staining, sugar reactions, Voges-Proskauer, citrate, and methyl-red tests to prove the absence of accidental contaminants (though in the conditions of working, with rather massive transfers at frequent intervals, such intruders would have stood little chance of establishing themselves).

One subculture represented about 8—10 generations.

For the less usual phenol derivatives we are indebted to Imperial Chemical Industries Limited.

Types of Behaviour on Training.—Type I is illustrated by the behaviour with phenol. Here the toxic agent lengthens the mean generation time without any serious increase in

the initial lag. After 100 subcultures in presence of phenol there is no definite improvement, but eventually a gradual shortening occurs as indicated in the summary in Table 1.

TABLE 1.

			Phenol, 700 mg./l.					
Subculture	1—50	50—100	100—200	215	221	248	263	} lag *ca.* 1 hr.
M.g.t., min.	45·5 ± 1·5	42 ± 2·0	38 ± 3·0	38	35	39	38	
			Phenol, 1100 mg./l.					
Subculture	1—50	50—100	100—150	180	204	219		} lag *ca.* 2·5 hr.
M.g.t., min.	72 ± 5·0	60 ± 4·5	52·5 ± 3·0	57	49	54		

Type II is illustrated by the behaviour with thymol. This is active at much lower concentrations than phenol, and the most marked effect is to cause an extremely prolonged initial lag phase. After the first subculture, however, there is already a marked improvement and after a few more the lag has been largely eliminated. The values of the m.g.t., however, fluctuate markedly and there is no apparent tendency towards attainment of an optimum growth rate (Table 2).

TABLE 2.

			p-Cresol, 500 mg./l.					
Subculture	1—40	40—80	115	150				} lag *ca.* 1 hr.
M.g.t., min.	58 ± 2·0	48·5 ± 2·5	44	40				
			p-Cresol, 600 mg./l.					
Subculture	1—20	20—45	45—100	173	178	188		} lag *ca.* 1·5 hr.
M.g.t., min.	75 ± 5·0	54·5 ± 3·5	48 ± 4·0	53	48	52		
			m-Cresol, 300 mg./l.					
Subculture	1—30	30—80	107	143				} lag *ca.* 1 hr.
M.g.t., min.	46 ± 3·0	46 ± 2·0	33	34				
			m-Cresol, 600 mg./l.					
Subculture	1—50	50—100	100—160	170	181			} lag *ca.* 1·5 hr.
M.g.t., min.	66 ± 4·0	50 ± 4·0	47·5 ± 2·5	40	50			
			o-Cresol, 300 mg./l.					
Subculture	1—40	40—70	93	128				} lag *ca.* 1·5 hr.
Mg.t., min.	44·5 ± 2·5	38·5 ± 2·5	31	31				
			o-Cresol, 500 mg./l.					
Subculture	1—30	30—60	83	119				} lag *ca.* 1 hr.
M.g.t., min.	59 ± 4·0	49 ± 2·0	44	46				
			o-Ethylphenol, 200 mg./l.					
Subculture	1—10	10—40	49	59				} lag *ca.* 0·5 hr.
M.g.t., min.	47·5 ± 1·5	46 ± 1·0	37	38				
			Cf. Thymol, 140 mg./l.					

Subculture	1	5	10	15	20	25	35	50	60	} (for lags see Fig. 1)
M.g.t., min.	44	46	55	42	38	40	34	45	44	

There are thus two major actions of the phenols, first to cause a general slowing of growth, against which adaptive response is slow and difficult, and secondly, to cause a long lag phase which is very readily eliminated by training.

The progressive reduction of the lag is shown for thymol and carvacrol in Fig. 1. This ready adaptive response is the most striking effect observed.

After being trained, the bacteria may be transferred to higher concentrations before an equivalent lag appears, as is shown in Fig. 2. In general, the trained strains will grow in concentrations about double those which proved completely inhibitory to growth of the untrained strain.

Comparison of Different Alkyl-substituted Phenols.—A conspectus of the results is given in Fig. 3 from which it appears that there are all gradations in behaviour from that of type I to that of type II.

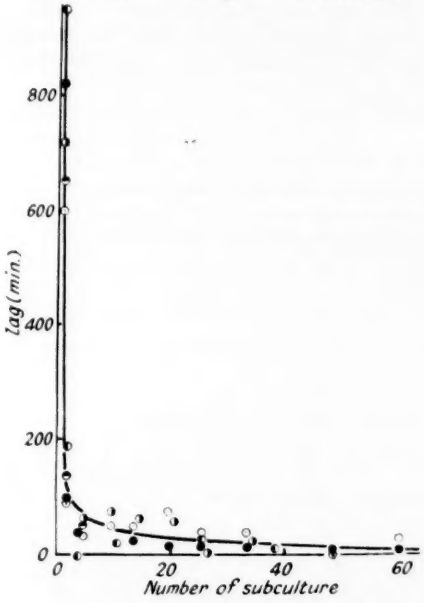
In general and in conformity with the findings of other authors the bacteriostatic action of the compound is found to increase with their molecular weight (cf. Suter, *Chem. Reviews*, 1941, **28**, 269; *Arch. Biochem. and Biophys.*, 1952, **40**, 306). But over and

above this, with passage from phenol and the lower alkylphenols towards the higher alkylphenols, there is a marked enhancement of the type-II behaviour.

All but one of the higher compounds tested have, however, branched alkyl chains, and comparison with *o*-butylphenol suggests that the branching may be more important in this respect than the increased molecular weight.

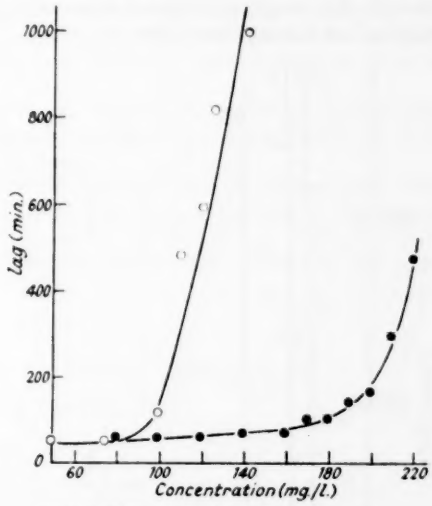
As the action of the compound becomes more pronounced, so in general the training becomes easier. Resistance to the cresols and to ethylphenols develops more rapidly and

FIG. 1. *Decrease in lag on serial subculture.*



Thymol, 110—200 mg./l.
Carvacrol, 140 mg./l.

FIG. 2. *Lag as function of thymol concentration.*



Open circles—untrained strain.
Full circles—strain trained to 200 mg./l. of thymol.

in greater degree than to phenol itself, as is evident from the summary in Table 2, where the progressive shortening of the generation times is shown. The elimination of the very long lags characteristic of type II behaviour occurs most rapidly of all (Table 3).

TABLE 3.

Phenol	Concn., mg./l.	Lag (min.) at 1st Subculture	Lag (min.) at 2nd Subculture	Lag (min.) of trained strain
*o-iso*Propyl-	180	930	350	50 (6th sub.)
p-sec.-Amyl-	150	900	300	100 (10th ,,)
p-tert.-Amyl-	140	1000	200	50 (15th ,,)
o-n-Butyl-	100	700	700	120 (10th ,,)
Thymol	140	750	100	40 (20th ,,)

Cross Resistance.—When the bacteria have been trained to resist any of the substances with which they show type-II behaviour, they are found also to resist others of the same group; for example, strains trained to grow without lag in thymol (140 mg./l.), *p-tert.*-amylphenol (150 mg./l.), or *o-iso*propylphenol (180 mg./l.) would also grow without lag in any of the others. This is the most clear-cut result. Apart from this there are other cross relationships, but of a rather complex and somewhat indefinite kind. It seems that some phenols constitute an intermediate class, *e.g.*, training to *o-iso*propylphenol provokes a partial resitance both to phenol itself and to thymol.

Stability of Training.—Determination of the growth rates in the ordinary medium of

the strains trained to phenol, *m*- and *p*-cresol, and ethylphenol shows that all are undamaged, even after many passages through the drug (250 in the case of phenol).

TABLE 4.

Training	M.g.t. (min.) on re-test in drug medium: After 1 subculture in drug-free medium	After 10 subculture in drug-free medium	Untrained strain
209 subcultures in phenol at 1100 mg./l. ...	49	59	71
178 subcultures in *p*-cresol at 600 mg./l.	48	57	82
170 subcultures in *m*-cresol at 600 mg./l.....	40	50	70
49 subcultures in ethylphenol at 200 mg./l....	37	54	49

Further determinations in the appropriate drugs of growth rates after ten passages through the drug-free medium show that fairly rapid though not yet complete loss of training has taken place (Table 4).

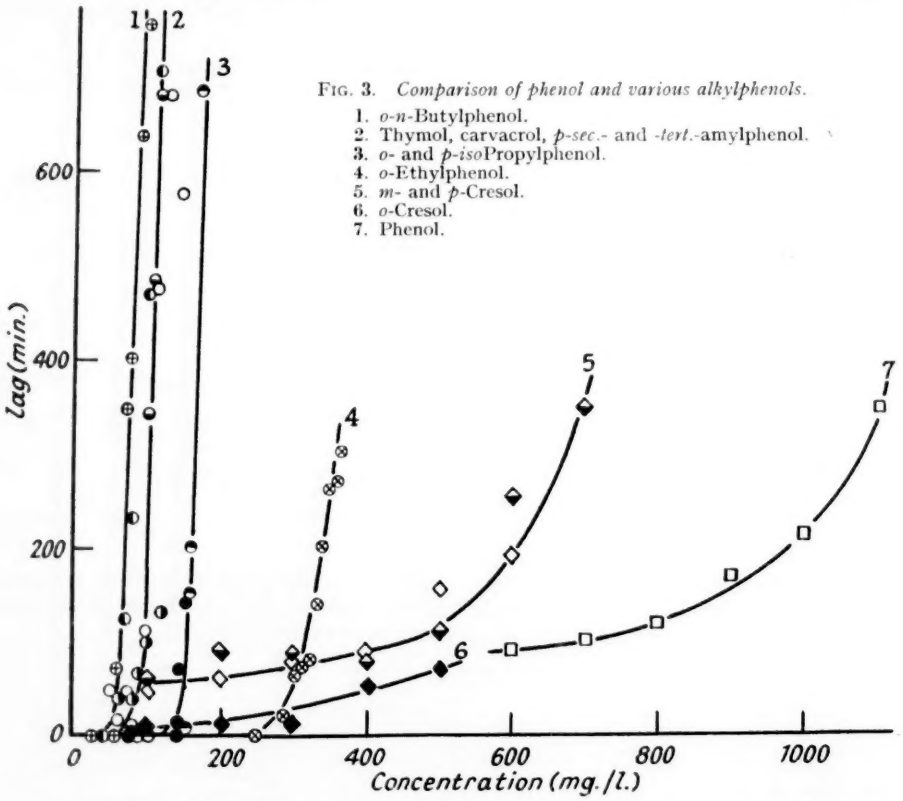


FIG. 3. *Comparison of phenol and various alkylphenols.*

1. *o-n*-Butylphenol.
2. Thymol, carvacrol, *p-sec.*- and *-tert.*-amylphenol.
3. *o*- and *p-iso*Propylphenol.
4. *o*-Ethylphenol.
5. *m*- and *p*-Cresol.
6. *o*-Cresol.
7. Phenol.

Results on the detraining of a thymol-resistant strain are given in Table 5. The loss of resistance (shown by increase in lag) occurs less readily the longer the original training has been continued.

TABLE 5.

Subcultures in thymol (140 mg./l.)	Lags (min.) tested in thymol after various numbers of subcultures in drug-free medium: 0	1	2	3	4	5	6
0	950	—	—	—	—	—	—
1	150	—	—	810	—	900	—
4	100	—	—	—	850	730	—
7	40	—	440	—	700	—	—
10	60	360	—	260	330	200	240
27	40	150	140	—	135	150	—

DISCUSSION

The substances belonging to the group of which thymol is typical are active at much lower concentrations than phenol itself. This will be partly due to their higher molecular weight, which, according to well-known principles, affects their solubility in the cell substance in the direction causing greater toxicity. But this factor by itself is far from being the only important one, and does not account at all for the qualitative differences in the mode of action and in the response of the bacterium in the two types of case.

The substances like thymol cause a very long initial lag which is easily eliminated by training. Phenol is quite different. Thus the thymol-like action seems to be characteristic not so much of a phenol as of a compound possessing a branched alkyl chain, which the hydroxyl group, by making the molecule soluble, makes available in the medium.

The rapid training may well be an adaptation, not to true phenolic action, but to the effect of this side-chain. Thymol does indeed act upon the trained bacteria in a way generally similar to that of phenol.

Cells might acquire resistance by developing the capacity for removing the side-chain, but this view is too simple to account for all the facts in so far as the behaviour of the trained strains themselves is rather varied and complex.

At least it seems justifiable to conclude that the branched side-chains have two actions with untrained cells: they modify the partition coefficients so as to increase the phenolic action, and, in addition, they exert an inhibitory action of their own. With thymol and similar phenols this action is the more important, though readily removed by training.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, July 7th*, 1953.]

740. *Steroids. Part VI.* Partial Synthesis of 9 : 11-Dehydroprogesterone.*

By A. RUFF, C. W. SHOPPEE, and (in part) G. H. R. SUMMERS.

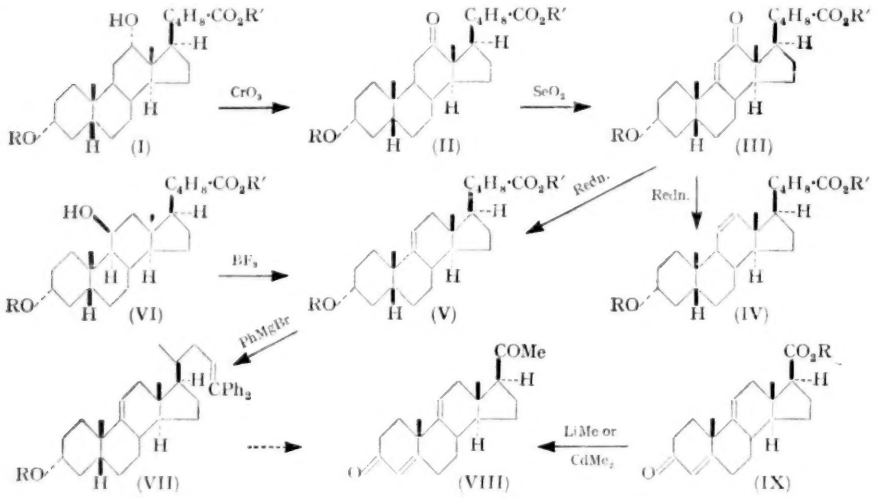
Attempted application of the Miescher–Wettstein degradation to 3α-hydroxychol-9(11)-enoic acid (9 : 11-dehydrolithocholic acid) failed to give 3α-hydroxypregn-9(11)-en-20-one, but by use of 3-oxoetia-4 : 9(11)-dienoic acid the partial synthesis of 9 : 11-dehydroprogesterone has been accomplished.

PROGESTATIONAL activity is a highly specific property; in addition to progesterone (the standard ≡ 1), only seven steroids exhibit comparable activity by subcutaneous application. These are the higher and lower homologues 17α-methylprogesterone (≡ 2) (Plattner, Heusser, and Herzig, *Helv. Chim. Acta*, 1949, **32**, 270; Heusser, Engel, Herzig, and Plattner, *ibid.*, 1950, **33**, 2229, 2237), 19-norprogesterone (≡ 1) (Miramontes, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1951, **73**, 3540), 6β-acetoxyprogesterone (≡ $< \frac{1}{4}$) (Ehrenstein and Stevens, *J. Org. Chem.*, 1940, **5**, 318; Balant and Ehrenstein, *ibid.*, 1952, **17**, 1587), 17α-ethynyltestosterone (Inhoffen and Hohlweg, *Naturwiss.*, 1938, **26**, 96; Ruzicka, Hofmann, and Meldahl, *Helv. Chim. Acta*, 1938, **21**, 371), and 6 : 7- (≡ $\frac{1}{2}$) (Wettstein, *ibid.*, 1940, **23**, 388; *Experientia*, 1946, **2**, 408), 9 : 11- (VIII) (≡ $> \frac{1}{2}$) (Shoppee and Reichstein, *Helv. Chim. Acta*, 1941, **24**, 351), and 11 : 12-dehydroprogesterone (≡ 3) (Hegner and Reichstein, *ibid.*, 1943, **26**, 715; von Euw and Reichstein, *ibid.*, 1946, **29**, 669; Meystre, Tschopp, and Wettstein, *ibid.*, 1948, **31**, 1463). Since the position assigned to the double bond in ring C of (VIII) is based on analogy and non-identity with 11 : 12-dehydroprogesterone, it seemed desirable to confirm the structure by partial synthesis.

Steroid 20-ketones are obtainable by degradation of bile acids or sapogenins. When this work was commenced (1949), deoxycholic acid (I*a*) was the only starting material available, and we converted it into 3α-hydroxychol-9(11)-enoic acid (V*a*) for degradation by the Miescher–Wettstein procedure to 3α-hydroxypreg-9(11)-en-20-one. Deoxycholic acid as the 3α-benzoyloxy-methyl ester (I*b*) with chromium trioxide in chlorobenzene–acetic

* Part V, *J.*, 1953, 2983.

acid at 20° (ref. b; references in this form are found in the Table) gave methyl 3α-benzoyloxy-12-oxocholanoate (II*b*) accompanied by the anhydride of the free hydroxy-acid (II*a*), and methyl 3 : 12-dioxocholanoate. By dehydrogenation with selenium dioxide



	M. p.	$[\alpha]_D$	Refs.
I*a*; R = R′ = H	176°	+ 53°E	a, b
I*b*; R = Bz, R′ = Me...	110	—	b
II*a*; R = R′ = H	164	+110E	a, c, e
II*b*; R = Bz, R′ = Me	96/104/128	—	b, e, f
III*a*; R = R′ = H	180	+107M	b, d, e, g
III*b*; R = Ac, R′ = Me	148	+111C	e, g, h, i
III*c*; R = Bz, R′ = Me	125	+126C	f
IV*a*; R = R′ = H	165	+ 43E	j
IV*b*; R = H, R′ = Me	106	+ 46M	k, l
IV*c*; R = Ac, R′ = Me	119	+ 51A	k, l
IV*d*; R = Bz, R′ = Me	Not isolated		f
V*a*; R = R′ = H	190	+47E	c, e, g, h
V*b*; R = H, R′ = Me	105°/113°	+45°A, +46M	g, h
V*c*; R = Ac, R′ = Me	138	+57C, +63A	e, g, h, m
V*d*; R = Bz, R′ = Me	Amorphous		f
VI*a*; R = R′ = H ...	200	+ 55M	m
VI*b*; R = Ac, R′ = Me	147	+ 71A	m, n, o
VII*a*; R = H	Amorphous		f
VII*b*; R = Ac	142	+ 79C	f
VIII	125	+159A	f, p
IX*a*; R = H	240 *	—	q
IX*b*; R = Me	105	+132C	q

A = Acetone; C = chloroform; E = ethanol; M = methanol. * With decomp.

References: a, M. Sorkin and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 797. b, McKenzie, Mattox, Engel, and Kendall, *J. Biol. Chem.*, 1948, **173**, 271. c, Chakravorty and Wallis, *J. Amer. Chem. Soc.*, 1940, **62**, 318. d, Longwell and Wintersteiner, *ibid.*, p. 200. e, Hicks, Berg, and Wallis, *J. Biol. Chem.*, 1946, **162**, 633. f, This paper. g, Seebeck and Reichstein, *Helv. Chim. Acta*, 1943, **23**, 536. h, Mattox, Turner, Engel, McKenzie, McGuckin, and Kendall, *J. Biol. Chem.*, 1946, **164**, 569. i, Turner, Mattox, Engel, McKenzie, and Kendall, *ibid.*, 1946, **162**, 571. j, McKenzie, McGuckin, and Kendall, *ibid.*, 1946, **162**, 555. k, Engel, Mattox, McKenzie, McGuckin, and Kendall, *ibid.*, p. 565. l, Press and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 878. m, Turner, Mattox, Engel, McKenzie, and Kendall, *J. Biol. Chem.*, 1946, **166**, 345. n, Lardon and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 586. o, Ott and Reichstein, *ibid.*, p. 1799. p, Shoppee and Reichstein, *ibid.*, 1941, **24**, 351. q, Casanova, Shoppee, and Summers, *J.*, 1953, 2983.

in chlorobenzene–acetic acid (Schwenk and Stahl, *Arch. Biochem.*, 1947, **14**, 125; ref. b) methyl 3α-benzoyloxy-12-oxocholanoate (II*b*) gave methyl 3α-benzoyloxy-12-oxochol-9(11)-enoate (III*c*), giving no m. p. depression with the saturated 3α-benzoyloxy-methyl ester (II*b*), or, after hydrolysis, 3α-hydroxy-12-oxochol-9(11)-enoic acid (III*a*) (refs. b, d, e, g). Subsequently, Fieser and Rajagopalan (*J. Amer. Chem. Soc.*, 1950, **72**, 5530) have recommended the use of 3α-ethoxycarbonyl derivatives in the reaction sequence (I ⟶ II ⟶ III), whilst a new route from cholic acid to the acid (III*a*) has been described by Fieser, Tishler, *et al.* (*ibid.*, 1951, **73**, 4133).

Methyl 3α-benzoyloxy-12-oxochol-9(11)-enoate (III*c*) was reduced by the Wolff–Kishner reaction, under pressure or at low pressure in triethylene glycol, to a mixture of

3α-hydroxychol-11-enoic acid (IV*a*) and 3α-hydroxychol-9(11)-enoic acid (V*a*). It is known that Wolff–Kishner reduction of $\Delta^{9(11)}$-12-ketones gives mixtures of 11- and 9(11)-unsaturated acids (Alther and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 492); thus, the 3α-hydroxy-acid (III*a*), its 3α-acetoxy-methyl ester (IIIb), and its 3α-ethoxycarbonyl-methyl ester * also afford a mixture of the acids (IV*a*, V*a*). These acids and their 3α-acetoxy-methyl esters are isomorphous with each other and with 3α-hydroxycholanoic [≡ lithocholic] acid and its acetoxy-methyl ester. Reichstein and Seebeck (ref. g., p. 536, footnote 2) noted that the methyl esters (IV*b*, V*b*) are not isomorphous and give a small but definite m. p. depression; we were able to effect a partial separation of these esters by fractional crystallisation from methanol. A similar, nearly complete separation has subsequently been reported by Fieser and Rajagopalan (*loc. cit.*). A previous attempt to separate the 3α-acetoxy-methyl esters (IV*c*, V*c*) by use of bromine (1 mol.) was unsuccessful (ref. g.); we have confirmed this but we have been able completely to remove the 3α-acetoxy-methyl ester (IV*c*) by partial bromination (0·2 mol.). Although (V*c*) reacts with bromine to undergo deep-seated change (cf. ref. h), (IV*c*) undergoes addition to give methyl 3α-acetoxy-11β : 12α-dibromocholanoate (refs. h, o; Kendall *et al.*, *J. Biol. Chem.*, 1948, **172**, 283); this is readily separated chromatographically from the unchanged 3α-acetoxy-methyl ester (V*c*) and by debromination with zinc–acetic acid affords the pure ester (IV*c*). The 3α-benzoyloxy-methyl esters (IV*d* and V*d*) may be separated similarly.

Alternatively, the 3α-benzoyloxy-methyl ester (III*c*) by condensation with ethanedithiol gave a quantitative yield of the 12-mercaptal, desulphurised with Raney nickel in ethanol to a product which was separated chromatographically into an unidentified substance and methyl 3α-benzoyloxychol-9(11)-enoate (V*d*); this was converted by hydrolysis, esterification, and acetylation into the pure 3α-acetoxy-methyl ester (V*c*), identical with a specimen prepared some 10 years ago by dehydration of methyl 3α-acetoxy-11β-hydroxycholanoate (VI) with boron trifluoride in acetic acid–acetic anhydride at 20° (Shoppee, *Helv. Chim. Acta*, 1943, **27**, 543; cf. Heymann and Fieser, *J. Amer. Chem. Soc.*, 1951, **73**, 5252).

By treatment with phenylmagnesium bromide methyl 3α-acetoxychol-9(11)-enoate (V*c*) gave 24 : 24-diphenylchol-9(11)-ene-3α : 24-diol; this was acetylated with acetic anhydride–pyridine, at 20° and the 3α-monoacetate dehydrated by refluxing acetic acid (Morsman, Steiger, and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 1) to 3α-acetoxy-24 : 24-diphenylchola-9(11) : 23-diene (VII).†

The action of *N*-bromosuccinimide in non-polar solvents on allylic systems is catalysed photochemically (Miescher *et al.*, *Helv. Chim. Acta*, 1945, **28**, 1252) and by peroxides (Karrer and Schmid, *ibid.*, 1946, **29**, 573), and appears to involve succinimidoyl radicals for chain-propagation (Dewar, " Electronic Theory of Organic Chemistry," Oxford, 1949, p. 273), since there is attack at the α-methylene group but not at the double bond as would be expected with bromine atoms. Since tertiary hydrogen atoms are not attacked (Ziegler *et al.*, *Annalen*, 1942, **551**, 80; Miescher *et al.*, *loc. cit.*), except in the presence of peroxide (Karrer and Schmid, *loc. cit.*), it was expected that treatment of 3α-acetoxy-24 : 24-diphenylchola-9(11) : 23-diene (VII) with *N*-bromosuccinimide in carbon tetrachloride would lead

* This pure compound, m. p. 158—161°, $\lambda_{max.}$ 239, log ε 4·05—4·10, by Wolff–Kishner reduction gave a product which, after esterification with diazomethane, acetylation, and treatment with perbenzoic acid, was resolved chromatographically into methyl 3α-acetoxycholanoate (30%), the 11α : 12α-epoxide of (IV*c*) (16%), and the 9α : 11α-epoxide of (V*c*) (34—41%). The presence of 30% of 3α-hydroxycholanoic acid in the reduction product seems improbable. We have found that pure methyl 3α-acetoxychol-9(11)-enoate does not react quantitatively with perbenzoic acid at 0°, although Seebeck and Reichstein (ref. g) observed a quantitative reaction at 18°. Fieser and Rajagopalan (*loc. cit.*) do not state their conditions for epoxidation or how their unoxidised product was identified as methyl 3α-acetoxycholanoate; we believe that their unoxidised product was methyl 3α-acetoxychol-9(11)-enoate (V*c*), since the difference in m. p. of these isomorphous compounds is only 4° (ref. g).

† This compound exhibits $\lambda_{max.}$ 206 mμ, log ε 4·51 and $\lambda_{max.}$ 253 mμ, log ε 4·24. The latter maximum arises from the 24 : 24-diphenylethylene grouping (cf. Coles and Braude, *J.*, 1950, 2016); the former is probably due to the two phenyl groups [cf. toluene with $\lambda_{max.}$ 206 mμ, log ε 3·90 (Bowden and Braude, *J.*, 1952, 1068)], whilst the large extinction coefficient appears to be due to a contribution from ethylenic double bond absorption, since a new determination of the ultra-violet spectrum of 1 : 1-diphenylethylene by Dr. Braude shows maxima at 208 mμ, log ε 4·20, 228 mμ, log ε 4·17, and 251 mμ, log ε 4·04. We wish to thank Dr. E. A. Braude for a private discussion and for his kindness in making available his new unpublished results on 1 : 1-diphenylethylene.

to substitution at $C_{(22)}$ in the side-chain under the activating influence of the $C_{(24)}$-phenyl groups rather than at $C_{(12)}$ in the nucleus. In exploratory experiments, the 3α-acetoxymethyl ester (V*c*) was briefly treated with pure *N*-bromosuccinimide (0·75 mol.) in carbon tetrachloride whereby succinimide was formed and 65—70% of the starting material recovered by crystallisation or chromatography; no other crystalline products could be isolated. To determine whether attack at $C_{(12)}$ was taking place, the 3α-hydroxy-methyl ester (V*b*) was similarly treated with *N*-bromosuccinimide; here substitution at $C_{(12)}$ should yield the labile methyl 3α-hydroxy-12α-bromochol-9(11)-enoate, quantitatively converted by treatment in chloroform solution with cold water into the stable methyl 3α : 9α-epoxychol-11-enate, m. p. 53°, $[\alpha]_D$ −58°, which furnishes stable epimeric 11β : 12α- and 11α : 12β-dibromides (Kendall *et al.*, ref. h, *J. Biol. Chem.*, 1948, **173**, 283). Succinimide was again formed, and 60% of the starting material was recovered but methyl 3α : 9α-epoxychol-11-enate could not be isolated.*

The 3α-acetoxy-9(11) : 23-diene (VII) with *N*-bromosuccinimide in carbon tetrachloride under various conditions gave succinimide, but ~70% of unchanged starting material was the only crystalline product which could be isolated. The residual material consisted of uncrystallisable oils, showing no selective absorption in the 205-mμ region, and taking up only 1·04 mol. of perbenzoic acid to give a non-crystalline 3α-acetoxy-23 : 24-epoxide, reduced by lithium aluminium hydride to a non-crystalline product (probably a 3α : 24-diol). These results suggest disappearance or migration of the 9(11)-double bond. Miescher, Wettstein, *et al.* (*Helv. Chim. Acta*, 1946, **29**, 627; 1947, **30**, 1022) were able to protect a 5(6)-double bond in a 3β-acetoxy-5 : 23-diene, before treatment with *N*-bromosuccinimide, by addition of hydrogen chloride; we find that the 9(11)-double bond in the ester (V*c*) or the diene (VII) fails to add hydrogen chloride (cf. ref. b, p. 278, footnote 8), whilst the attractive alternative of temporary protection by peroxidation: $>\underset{(9)}{C}=\underset{(11)}{CH}- \longrightarrow >C\overset{O}{\diagdown\!\diagup}CH- \longrightarrow >C(OH)\cdot CH_2- \longrightarrow >C{:}CH-$ is precluded by the stability of 9α : 11α-epoxides to lithium aluminium hydride (Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1951, **73**, 118).

It appears then that the Miescher–Wettstein procedure cannot be applied to $\Delta^{9(11)}$-steroids, and it seems improbable that the Barbier–Wieland degradation can be used since it involves oxidation with chromium trioxide, which converts $\Delta^{9(11)}$-steroids into $\Delta^{9(11)}$-12-ketones and 9α : 11α-epoxides (Reichstein *et al.*, *Helv. Chim. Acta*, 1943, **26**, 492, 536; 1945, **28**, 1420; Reich and Lardon, *ibid.*, 1947, **30**, 329; Shoppee, *ibid.*, p. 766).

We were therefore compelled to resort to the alternative route investigated by Casanova, Shoppee, and Summers (*J.*, 1953, 2983), whereby the side-chain of deoxycholic acid is removed before introduction of the 9(11)-double bond. Deoxycholic acid was degraded to 3-oxoetia-4 : 9(11)-dienoic acid (IX), which by treatment with methyl-lithium or, better, as the acid chloride with dimethylcadmium, gave 9 : 11-dehydroprogesterone (VIII), m. p. 125°, $\lambda_{max.}$ 240 (log ε 4·15) (≡ Δ^4-3-oxo-grouping) and 206 mμ (log ε 3·67) (≡ $R_2C_{(9)}{:}CH_{(11)}\cdot$) (cf. Henbest *et al.*, *Chem. and Ind.*, 1951, 866; *J.*, 1952, 2737), exhibiting bands in the infra-red spectrum at 1730 (≡ 20-oxo-group) and 1675 cm.$^{-1}$ (≡ Δ^4-3-oxo-group), which did not depress the m. p. of a specimen prepared by one of us in 1941 by dehydration of 11β-hydroxyprogesterone (Reichstein and Fuchs, *Helv. Chim. Acta*, 1940, **23**, 684; Shoppee and Reichstein, ref. p; Rosenkranz *et al.*, *J. Org. Chem.*, 1952, **17**, 290) with hydrogen chloride–acetic acid.† This partial synthesis establishes the structure originally assigned.

Experimental

For general directions see *J.*, 1953, **243**, 540; $[\alpha]_D$ are determined in $CHCl_3$ and ultra-violet spectra in ethanol, a Unicam SP. 500 spectrometer with corrected scale being used. References

* In a German patent U 1313/120 25/05, dated 1.ix.51, it is claimed that treatment of the 5α : 8α-maleic anhydride adduct of 3β-acetoxypregna-5 : 7 : 9(11)-trien-20-one with *N*-bromosuccinimide in irradiated carbon tetrachloride gives a crystalline 12-bromo-drivative.

† Analogy suggests that this preparation, m. p. 121°, may contain traces of 11 : 12-dehydroprogesterone since these isomerides are probably isomorphous. 11α-Hydroxyprogesterone resists dehydration by acetic anhydride at 100° and gives the 11α-acetate (Rosenkranz *et al.*, *J. Org. Chem.*, 1952, **17**, 1066).

denoted by letters are those of the table on p. 3684, where previously recorded constants are also given.

Methyl 3α-*Benzoyloxy*-12-*oxocholanoate* (II*b*).—Methyl 3α : 12α-dihydroxycholanoate (ref. a) was converted into the 3α-benzoate, which was oxidised with chromium trioxide in chlorobenzene at 20—25° according to the directions of Kendall *et al.* (ref. b). Crystallisation of the oxidation product from acetone–methanol led to the separation of a by-product, which was removed by filtration; the filtrate, cooled to 5°, gave methyl 3α-benzoyloxy-12-oxocholanoate (form A) in plates, m. p. 92—96°, after recrystallisation from methanol. Another run furnished form B, needles (from methanol), m. p. 100—104°, which gave no depression (m. p. 92—104°) by admixture with form A. Form A, dissolved in methanol and inoculated with B, gave form B in long needles, m. p. 100—104°; conversely, a methanolic solution of form B seeded with A gave form A in plates, m. p. 92—96°. A solution of form B in methanol inoculated with authentic methyl 3α-benzoyloxy-12-oxocholanoate (form C), m. p. 126—128°, kindly supplied by Professor E. C. Kendall, gave form C in prisms, m. p. 126—128°; conversion of C into A or B was difficult and succeeded only once, when a hot saturated solution of C in methanol was added slowly to crystals of B. Both form A and form B were stable to further oxidation, gave 3α-hydroxycholanoic acid by low-pressure Wolff–Kishner reduction, and furnished by complete hydrolysis and re-esterification with diazomethane methyl 3α-hydroxy-12-oxocholanoate, m. p. 111° [Sawlewicz and Reichstein (*Helv. Chim. Acta*, 1937, **20**, 992) give m. p. 112°]; subsequently, it was found that form A had been encountered incidentally by Hicks, Berg, and Wallis (ref. e, p. 638). Before a specimen of form C was obtained from the U.S.A., repeated recrystallisation of form B always gave form B; from the time that form C was introduced into the laboratories, all further oxidations (I*b* ⟶ II*b*) gave form C.

The by-product, purified by chromatography on aluminium oxide by elution with benzene and ether–benzene (1 : 1) and then by recrystallisation from chloroform–ether, was identified as 3α-*hydroxy*-12-*oxocholanoic anhydride*, m. p. 242—244°, $[\alpha]_D$ +119° ± 1° (*c*, 5·67) (Found, after drying at 90°/0·05 mm. for 2 hr.: C, 75·6; H, 9·7. $C_{48}H_{74}O_7$ requires C, 76·0; H, 9·4%). The united mother-liquors from several oxidations, by chromatography on aluminium oxide, after elution with benzene–pentane (1 : 1) and benzene, gave methyl 3α-benzoyloxy-12-oxocholanoate (II*b*), m. p. 126—128°, by elution with ether–benzene (1 : 3 and 1 : 1), and with ether gave methyl 3 : 12-dioxocholanoate as prisms (from ether–pentane), m. p. 132—133° (Found, after drying at 70°/0·04 mm. for 2 hr.: C, 74·85; H, 9·3. Calc. for $C_{25}H_{38}O_4$: C, 75·1; H, 9·5%), depressed by admixture with (II*b*) to 102°; Reichstein *et al.* (refs. a, n) record m. p. 132—133°.

Methyl 3α-*Benzoyloxy*-12-*oxochol*-9(11)-*enoate* (III*c*).—Oxidation of methyl 3α-benzoyloxy-12-oxocholanoate (II*b*) with selenium dioxide–chlorobenzene–acetic acid by the method of Kendall *et al.* (ref. b) and hydrolysis gave a 72% yield of 3α-hydroxy-12-oxochol-9(11)-enoic acid (III*a*) (m. p. 176—178°; degree of unsaturation, ~85%) after 27 crystallisations from acetone and acetone–methanol–pentane. This material when purified by Kendall's sodium salt method gave 53% of pure 3α-hydroxy-12-oxochol-9(11)-enoic acid, m. p. 180—181°, $[\alpha]_D$ +100°, $\lambda_{max.}$ 240 mμ (log ε 4·07) (cf. Kendall *et al.*, ref. b). Alternatively, by omission of the alkaline hydrolysis stage, the crude 3α-benzoyloxy-methyl ester (III*c*) and the crude 3α-benzoyloxy-acid could be isolated; the crude acid was esterfied with 1% methanolic hydrogen chloride at 20° and the combined 3α-benzoyloxy-methyl esters, dissolved in ether, were passed through a column of aluminium oxide to give by repeated crystallisation from acetone–ether–pentane *methyl* 3α-*benzoyloxy*-12-*oxochol*-9(11)-*enoate* (III*c*), m. p. 123—125°, $[\alpha]_D^{20}$ +126·5° ± 2° (*c*, 1·02), $\lambda_{max.}$ 229 mμ (log ε 4·404) (Found, after drying at 60°/0·04 mm. for 2 hr.: C, 75·75; H, 8·5. $C_{32}H_{42}O_5$ requires C, 75·85; H, 8·35%), showing no m. p. depression on admixture with the saturated 3α-benzoyloxy-ester (II*b*), m. p. 126—128°, and giving no colour with tetranitromethane–chloroform.

Methyl 3α-*Acetoxychol*-9(11)-*enoate* (V*c*).—Methyl 3α-benzoyloxy-12-oxochol-9(11)-enoate (III*c*) by high-pressure Wolff–Kishner reduction gave a mixture of the 3α-hydroxy-acids (IV*a* and V*a*) in crystalline condition and good yield {mixed 3α-acetoxy-methyl esters, m. p. 126—132°, $[\alpha]_D^{18}$ + 62° (*c*, 1·10)}; use of the Huang-Minlon low-pressure procedure in ethylene glycol gave only a 40% yield, because the mixed acids could not be precipitated in crystalline form and extraction was difficult {mixed 3α-acetoxy-methyl esters, m. p. 126—132°, $[\alpha]_D^{20}$ +65° (*c*, 3·03)}, but good results were obtained in triethylene glycol (cf. Fieser and Rajagopalan, *J. Amer. Chem. Soc.*, 1951, **73**, 118) from which the mixed acids separated readily in crystals {mixed 3α-acetoxy-methyl esters, m. p. 134—136°, $[\alpha]_D$ +62° (*c*, 1·11)}. Similarly, 3α-hydroxy-12-oxochol-9(11)-enoic acid (III*a*) [m. p. 180—181°, $\lambda_{max.}$ 240 mμ (log ε 4·07)] in trimethylene

glycol gave 75—85% yields of the mixed acids (IV*a* and V*a*). Such a mixture (18·6 g.) was esterified in dioxan with ethereal diazomethane, and a sample of the product repeatedly crystallised from ether–pentane to give methyl 3α-hydroxychol-9(11)-enoate (V*b*) as needles, m. p. 105°, $[\alpha]_D$ +44° (*c*, 1·01) (refs. g, h). The greater part of the product was acetylated with acetic anhydride–pyridine at 20° to give, after crystallisation from acetone–methanol, a mixture of the 3α-acetoxy-methyl esters (IV*c* and V*c*) (17 g.), m. p. 134—136°. A specimen (1·18 g.) of the mixture, dissolved in chloroform (5 c.c.), was titrated at 15° with a solution of bromine (0·415 g., 1 mol.) in chloroform (2 c.c.), of which 0·40 c.c. was immediately decolourised. The solution was at once evaporated completely at 15°/10 mm. and 0·05 mm., and the residue chromatographed on aluminium oxide (18 g.) prepared in pentane. Elution with benzene–pentane (1 : 5; 1 : 3) gave the pure 3α-acetoxy-methyl ester (V*c*) (0·72 g.), m. p. 137—139°, $[\alpha]_D$ +63° (*c*, 1·01 in $COMe_2$), after recrystallisation from acetone–methanol. Elution with benzene–pentane (1 : 1) and with benzene gave methyl 3α-acetoxy-11β : 12α-dibromocholanoate (0·20 g.), m. p. 188—195° (decomp.) after recrystallisation from acetone–methanol {Kendall *et al.*, ref. k, give m. p. 195° (decomp.), $[\alpha]_D$ +65°}, debrominated with zinc–sodium acetate in acetic acid for 15 min. at 70° to give the pure 3α-acetoxy-methyl ester (IV*c*), m. p. 116—118°, $[\alpha]_D$ +50° (*c*, 1·04) (refs. k, l), after recrystallisation from acetone–methanol.

The pure ester (V*c*) (270 mg.; m. p. 137—139°) derived from the pure 3α-hydroxy-acid (III*a*) (with $\lambda_{max.}$ 240 mμ, log ε 4·07), dissolved in chloroform (2 c.c.), was treated with a solution of perbenzoic acid (110 mg., 1·3 mol.) in chloroform (1·5 c.c.) at 0° for 17 hr. After removal of chloroform at 30°/10 mm., the product was dissolved in ether, washed with dilute solutions of sodium iodide and sodium thiosulphate, water, 2N-Na_2CO_3, and water, dried, and evaporated. The crystalline residue was chromatographed on aluminium oxide (9 g.) in pentane; elution with benzene–pentane (1 : 3; 2 : 5) gave the unchanged ester (V*c*) (90 mg.), m. p. 136—138°, after recrystallisation from ether–pentane–methanol, giving a yellow colour with tetranitromethane–chloroform. Elution with benzene–pentane (3 : 2) and benzene gave methyl 3α-acetoxy-9α : 11α-epoxycholanoate (138 mg.), m. p. 118° after crystallisation from methanol {Seebeck and Reichstein (ref. g), give m. p. 121°, [α] +44°, whilst Hicks, Berg, and Wallis (*J. Biol. Chem.*, 1946, **162**, 645) give m. p. 118·5°}. The unaltered ester (V*c*) (90 mg.) was re-treated with perbenzoic acid (37 mg.) as above, and by chromatogrphy yielded the unchanged ester (V*c*) (15 mg.), m. p. 135—137°, and methyl 3α-acetoxy-9α : 11α-epoxycholanoate (55 mg.), m. p. 117°.

The pure ester (V*c*) (200 mg.; m. p. 137—139°) in chloroform (1 c.c.) was treated gradually with bromine (74 mg., 1 mol.) in chloroform (2 c.c.) at 18°. The first drop of bromine was not decolorised, and when approximately half of the bromine had been added production of hydrogen bromide could be observed. After addition of ether, the solution was washed with ice-cold N-sodium hydroxide and then water, dried, and evaporated, and the resultant yellow oil chromatographed on aluminium oxide (6 g.) in pentane. Elution with benzene–pentane (1 : 5; 2 : 5) gave the 3α-acetoxy-methyl ester (V*c*) (130 mg.), m. p. and mixed m. p. 136—138° (after recrystallisation from acetone–methanol), giving a yellow colour with tetranitromethane–chloroform. Further elution of the column gave uncrystallisable oils.

Treatment of the 3α-acetoxy-methyl ester (V*c*) (600 mg.; m. p. 136—138°) in chloroform–acetic acid (1 : 1) with dry hydrogen chloride at 0° failed to give a hydrochloride; the product consisted of unchanged ester, m. p. 134—136°, and partly hydrolysed material.

Methyl 3α-Benzoyloxychol-9(11)-enoate (V*d*).—(*a*) Methyl 3α-benzoyloxy-12-oxochol-9(11)-enoate (III*c*) (2 g., m. p. 123—125°; $\lambda_{max.}$ 228, log ε 4·40; dried at 100°/0·01 mm.) was partly dissolved in ethanedithiol (20 c.c.; b. p. 151—154°), and treated at −15° with dry hydrogen chloride (~20 c.c.) with exclusion of moisture. After 3 hr. at 0°, the mixture was neutralised with solid anhydrous sodium carbonate, and the product extracted with ether; the extract was washed with ice-cold 5N-sodium hydroxide and then water, dried, and evaporated. The residual oil was chromatographed on aluminium oxide (100 g.) prepared in pentane; the fractions eluted by benzene–pentane (1 : 1) and benzene furnished positive tests for sulphur and yellow colours with tetranitromethane–chloroform, but did not crystallise and were united. The colourless mercaptal (1·6 g.) in ethanol (250 c.c.) was refluxed for 6 hr. with Raney nickel (prepared from 80 g. of nickel–aluminium alloy according to Mozingo *et al.*, *J. Amer. Chem. Soc.*, 1943, **65**, 1013, except that, after addition of the alloy, the mixture was kept at 20° for 16 hr.); filtration and evaporation in a vacuum gave a colourless oil (1 g.) which was chromatographed on aluminium oxide (30 g.) prepared in pentane. Elution with benzene–pentane (1 : 5 ⟶ 1 : 1) yielded colourless oils, which did not crystallise but gave negative tests for sulphur and yellow colours with tetranitromethane–chloroform; these consisted essentially of the 3α-benzoyloxy-methyl ester (V*d*) (0·5 g.) since complete alkaline hydrolysis, re-esterification with ethereal diazo-

methane, and acetylation afforded the 3α-acetoxy-methyl ester (V*c*), m. p. 132°, $[\alpha]_D^{18}$ +57° (*c*, 2·054). Further elution with ether–benzene gave a colourless oil (0·25 g., negative sulphur, positive tetranitromethane test); this cannot have arisen by partial hydrolysis at $C_{(3)}$ since acetylation failed to give the 3α-acetoxy-methyl ester (V*c*), which crystallises readily.

(*b*) The mixture of 3α-hydroxy-methyl esters (IV*b* and V*b*) (0·46 g.) in pyridine (7 c.c.) was treated with pure benzoyl chloride (0·7 c.c.) at 20° for 2 hr. After working up (cf. Hegner and Reichstein, *Helv. Chim. Acta*, **1943**, **26**, 715, 721), chromatography of the product on aluminium oxide by elution with benzene–pentane (1 : 5, 1 : 4, 1 : 3, 1 : 1, 2 : 3) gave a colourless oil (0·42 g.), which was dissolved in chloroform (2 c.c.) and titrated at 18° with bromine (0·16 g., 1 mol.) in chloroform (1 c.c.) until immediate decolorisation ceased. The solution was at once evaporated completely at 18°/10 mm. and 0·05 mm. and the residue chromatographed on aluminium oxide (14 g.) prepared in pentane; elution with benzene–pentane (1 : 5, 3 : 10) gave methyl 3α-benzoyloxychol-9(11)-enoate (V*d*) (146 mg.) as a colourless oil distilling at 170°/0·02 mm. (halogen test negative, tetranitromethane test positive), which did not crystallise. Elution with benzene–pentane (2 : 5, 1 : 1) gave an oil (160 mg.) containing methyl 3α-benzoyloxy-11β : 12α-dibromocholanoate (halogen test positive, tetranitromethane test negative), whilst elution with benzene gave an unidentified substance (12 mg.), m. p. 144—146° after recrystallisation from acetone–methanol.

The non-crystalline 3α-benzoyloxy-methyl ester (V*d*) by complete alkaline hydrolysis, re-esterification with diazomethane, and acetylation gave the 3α-acetoxy-methyl ester (V*c*), m. p. 134—137°.

3α-*Acetoxy*-24 : 24-*diphenylchola*-9(11) : 23-*diene* (VII*b*).—The 3α-acetoxy-methyl ester (V*c*) (1 g.; m. p. 136°) in benzene (6·6 c.c.) was added to a hot solution of phenylmagnesium bromide [from bromobenzene (4·6 c.c.) and magnesium (1·05 g.)], and the mixture refluxed for 3·5 hr. After cooling, the mixture was poured into a saturated solution of ammonium chloride at 0°, and extracted with ether; the product, after hydrolysis with hot methanolic 3% potassium hydroxide, by the usual treatment gave crude 24 : 24-diphenylchol-9(11)-ene-3α : 24-diol. This was treated with acetic anhydride–pyridine at 20° for 15 hr., and the crude 3α-acetoxy-24 : 24-diphenylchol-9(11)-en-24-ol refluxed with acetic acid (15 c.c.) (cf. Morsman, Steiger, and Reichstein, *loc. cit.*) for 6 hr. The product, by recrystallisation from methanol, gave 3α-*acetoxy*-24 : 24-*diphenylchola*-9(11) : 23-*diene* (870 mg.) as colourless needles, m. p. 140—142°, $[\alpha]_D^{17}$ +79° ± 2° (*c*, 1·78), $\lambda_{max.}$ 206 (log ε 4·51) and 253 mμ (log ε 4·24) (Found, after drying at 60°/0·04 mm. for 5 hr.: C, 84·8; H, 9·0. $C_{38}H_{48}O_2$ requires C, 85·0; H, 9·0%). Chromatography of the material from the mother-liquor on aluminium oxide gave by elution with benzene–pentane (1 : 5, 2 : 5) a further quantity (190 mg.) of the diene, m. p. 139° after recrystallisation from ether–methanol. Elution with benzene–pentane (3 : 2) gave an unidentified substance (76 mg.), m. p. 153—155° after crystallisation from acetone–ether. The 3α-acetoxydiene, as expected, gave negative Rosenheim and Tortelli–Jaffé tests, but when the latter was modified by use of trichloroacetic acid in place of acetic acid gave a green colour.

9 : 11-*Dehydroprogesterone* (VIII).—(*a*) 3-Oxoetia-4 : 9(11)-dienic acid [m. p. 240—250° (decomp.); 54 mg.] (Casanova, Shoppee, and Summers, *loc. cit.*), dissolved in dry benzene (2 c.c.), was treated with oxalyl chloride (0·25 c.c.) at 0° and set aside for 1 hr. at 20°. Benzene and excess of oxalyl chloride were removed in a vacuum and the acid chloride subjected to azeotropic distillation with benzene. A solution of methylmagnesium bromide [from magnesium (0·25 g.)] in ether (25 c.c.) was refluxed with dry cadmium chloride (0·5 g.) for 1 hr. with rigorous exclusion of moisture. The above acid chloride was added in benzene (10 c.c.) to the solution of dimethylcadmium, and the mixture stirred under reflux for 1 hr. The mixture was cooled, then decomposed with ice-cold 2N-hydrochloric acid, and the product isolated in the usual way, as an oil (43 mg.) which was chromatographed on neutralised aluminium oxide (2 g.) prepared in pentane. After elution (5 c.c.) with pentane and benzene–pentane (1 : 19, 1 : 9) (fractions 1—13) had given only traces of oil, use of benzene–pentane (1 : 1) gave an oil (10 mg.) which failed to crystallise; use of benzene (fractions 16—20) gave an oil (15 mg.) which crystallised from methanol at 0° and had m. p. 110—117°. This material, by crystallisation from pentane containing a trace of ether, gave needles, m. p. 123°, separated in a centrifuge; recrystallisation gave 9 : 11-dehydroprogesterone (VIII) (7 mg.), m. p. 125°, $[\alpha]_D$ +159° ± 4° (*c*, 0·23 in $COMe_2$), $\lambda_{max.}$ 240 (log ε 4·15) and 206 mμ (log ε 3·67), which did not depress the m. p. of a genuine specimen.

(*b*) 3-Oxoetia-4 : 9(11)-dienic acid (20 mg.) in ether (5 c.c.) was shaken vigorously with ethereal methyl-lithium at 15—20° for 0·5 hr. After being kept at 0° for 1·5 hr., the mixture was poured into ice-cold 2N-hydrochloric acid. The neutral product, isolated in the usual way, was an oil;

the alkaline washings, by acidification, gave only a slight turbidity. Chromatography of the neutral oil on aluminium oxide (250 mg.) and elution with benzene–pentane (2 : 1) and benzene gave fractions which crystallised on inoculation, having m. p. 110—122° and 115—122°; mixed with a genuine specimen of 9 : 11-dehydroprogesterone these preparations had m. p. 110—120°, but were too small for further purification.

One of us (A. R.) acknowledges the support of Glaxo Laboratories Ltd., which enabled him to take part in this work. We thank Dr. F. T. Macrae, Glaxo Laboratories Ltd., for a gift of deoxycholic acid, Professor E. C. Kendall for a specimen of methyl 3α-benzoyloxy-12-oxocholanate, Professor T. Reichstein for one of methyl 3α-acetoxy-11β : 12α-dibromocholanate, and Dr. R. N. Haszeldine, Cambridge, for the infra-red spectrum.

UNIVERSITY COLLEGE OF SWANSEA, UNIVERSITY OF WALES. [*Received, July 17th*, 1953.]

---

741. *Determination of Electrokinetic Charge and Potential by the Sedimentation Method. Part VI.* Carborundum in Aqueous Solutions of Some Uni-univalent Electrolytes.*

By G. A. H. ELTON and J. W. MITCHELL.

Electrokinetic charges and potentials of carborundum surfaces in dilute aqueous solutions of various uni-univalent electrolytes are determined by the sedimentation method. The results are rather higher than those obtained by other workers, using the method of electro-osmosis. This is taken as confirmation of the theoretical prediction that the neglect of surface conductivity in the derivation of the Helmholtz–Smoluchowski equation for electro-osmosis may lead to considerable errors. The present results are used to obtain information concerning the relative magnitudes of the adsorption energies of some of the ions involved.

THIS paper gives the results of measurements by the sedimentation method (Elton, *Proc. Roy. Soc.*, 1949, *A*, **197**, 668; *J. Chem. Phys.*, 1951, **31**, 1317) of the electrokinetic charges and potentials of carborundum surfaces in dilute aqueous solutions of hydrochloric acid, nitric acid, potassium chloride, potassium nitrate, potassium hydroxide, and sodium chloride. Table 1 gives the values of the charge σ calculated as described previously (Dulin and Elton, Part I, *J.*, 1952, 286) from the measured velocities of sedimentation of homodisperse suspensions of carborundum powder in the solutions, and of ζ, the potential across the diffuse part of the double layer, obtained from σ in the usual manner (Dulin and Elton, *loc. cit.*; Part V, *loc. cit.*).

TABLE 1.*

	σ						ζ					
Concn. N	HCl	HNO_3	KCl	KNO_3	NaCl	KOH	HCl	HNO_3	KCl	KNO_3	NaCl	KOH
1×10^{-5}	505	420	590	450	565	435	113·7	104·9	122·0	104·8	119·9	106·7
2×10^{-5}	635	555	745	585	700	585	108·3	101·6	116·3	104·2	113·1	104·1
5×10^{-5}	900	775	1020	805	965	820	102·8	95·5	109·0	97·3	106·3	97·0
1×10^{-4}	1100	1000	1250	1040	1170	1065	95·5	90·9	101·9	92·8	98·6	89·7
2×10^{-4}	1365	1250	1505	1305	1440	1380	89·2	84·9	94·0	88·6	91·8	89·7
5×10^{-4}	1800	1730	1960	1880	1900	1820	80·5	77·7	84·5	82·5	83·0	80·5
1×10^{-3}	2260	2190	2420	2350	2360	2210	74·9	73·5	78·0	76·7	76·9	73·9
2×10^{-3}	2830	2750	3000	2940	2976	2620	69·3	68·0	72·0	71·1	71·5	65·9

* All the values of σ and ζ are negative.

Measurements of sedimentation velocity and conductivity were made in a cell of the type described by Benton and Elton (Part IV, *J.*, 1953, 2096). The results for potassium chloride were obtained by using two different homodisperse specimens of carborundum, in suspensions of widely differing particle concentration. The values of σ obtained from the two suspensions agreed to within 2% over the whole range of concentration, giving further

* Part V, Dulin and Elton, *J.*, 1953, 2099.

confirmation of the soundness of the method, and indicating that in such suspensions (containing $6{\cdot}0 \times 10^{-5}$ g./ml. and $1{\cdot}2 \times 10^{-4}$ g./ml.) negligible particle–particle interaction occurs (see also Elton and Hirschler, Part II, *J.*, 1952, 2953; Dulin and Elton, 1953, *loc. cit.*). Results for the other electrolytes were obtained by using a single homodisperse specimen in each case.

In order to be able to assess the likely effect of variation in the quality (conductivity) of the water used in these experiments on the results obtained, σ was determined in water containing various amounts of carbonic acid. (The only significant impurity in good-quality conductivity water is dissolved carbon dioxide—see, *e.g.*, Davies, "Conductivity of Solutions," Chapman and Hall, London, 1933.) The potential was calculated from σ in the same manner as for uni-univalent electrolytes, the small number of carbonate ions present having no significant effect on the potential (Benton and Elton, *loc. cit.*). The results obtained are shown in Table 2, the charge and potential being recorded as functions of κ, the conductivity of the water. It is seen that σ increases with κ, while ζ is approximately constant over a considerable range. The water used as solvent in the experiments on the various electrolytes (except potassium hydroxide, see below) was

TABLE 2.

κ, gemmho	0·2	0·4	0·6	0·8	1·0	1·5	2·0
σ, e.s.u.	169	243	360	421	473	553	570
ζ, mv	129·5	143·0	146·5	147·6	148·7	143·9	137·7

All the above values are negative.

"equilibrium" water of conductivity around 1 gemmho, depending on atmospheric conditions. Variation of $\pm 0{\cdot}2$ gemmho in the conductivity of the solvent will cause a variation of approximately ± 50 e.s.u. in the charge carried by carborundum in the solvent, but the error introduced into the results for σ for the electrolyte solutions will probably be considerably less than this as the "solvent charge" is not additive to the "solute charge" (see p. 3692). In fact, experiments carried out on different days, using a given electrolyte dissolved in two specimens of water differing in conductivity by up to 0·2 gemmho, gave results for σ in agreement to within 20 e.s.u. over the whole concentration range.

Discussion.—Few electrokinetic data for carborundum are available for comparison with this work. Fairbrother and Mastin (*J.*, 1924, **125**, 2319; 1925, **127**, 332) studied, *inter alia*, the electrokinetic potential of carborundum in hydrochloric acid and potassium chloride solutions, using the method of electro-osmosis through a plug of carborundum. In calculating ζ from their measurements, they used the simple Helmholtz–Smoluchowski electro-osmosis equation $V = \zeta\varepsilon E/(4\pi\eta)$, where V is the velocity of electro-osmosis under a potential gradient E, and ε and η are respectively the dielectric constant and the viscosity in the double layer, taken as equal to the bulk values. However, as pointed out by Overbeek and Wijga (*Rec. Trav. chim.*, 1946, **65**, 556), application of this equation to results obtained from measurements of electro-osmosis through plugs is likely to lead to erroneous values of ζ, since it makes no allowance for the effect of surface conductance. Table 3 gives a comparison of our results for ζ in hydrochloric acid and potassium chloride solutions

TABLE 3.

Concentration, N ...	2×10^{-5}	5×10^{-5}	1×10^{-4}	2×10^{-4}	5×10^{-4}	1×10^{-3}	2×10^{-3}
$\zeta_{\text{electro-osmosis}}/\zeta_{\text{sedimentation}}$ HCl	0·554	0·496	0·461	0·421	0·385	0·334	0·289
KCl	0·628	0·624	0·648	0·670	0·710	0·718	0·694

with Fairbrother and Mastin's at suitably interpolated concentrations. It is seen that the values of ζ in potassium chloride solution from electro-osmosis are about 30% lower than from sedimentation velocity over the entire concentration range, while for hydrochloric acid the values from electro-osmosis are about 40% lower in the most dilute solutions, and the difference increases steadily to 70% in the most concentrated solutions. It would appear likely from this that the effect of surface conductance on the electro-osmosis is considerable, and is relatively greater in hydrochloric acid than in potassium chloride solutions, especially at the higher concentrations.

Elton (1949, *loc. cit.*) studied the effect of electroviscosity on the velocity of sedimentation of carborundum particles in potassium chloride solutions, before the theory for non-spherical particles had been adequately developed. In order to estimate the order of the electrokinetic potentials, he assumed that the carborundum particles could be treated as spheres, and used a simple expression for the electroviscosity which, as he pointed out, will lead to high values for ζ. His values are, in fact, roughly twice those obtained by using the full expression for non-spherical particles.

It is seen from Table 1 that the charges in potassium chloride and sodium chloride solutions differ only very slightly over the whole range, those in potassium chloride solution being slightly the larger. This indicates that the potassium and the sodium ion possess similar adsorption energies at the carborundum surfaces, that for the potassium ion being slightly the smaller (*i.e.*, more negative). This has been confirmed by measurements of ion adsorption (Elton and Mitchell, unpublished work), the values being $-7{\cdot}3$ kcal. for the potassium ion, and $-7{\cdot}2$ kcal. for the sodium ion, for adsorption from 10^{-3}N-solutions.

The charge in hydrochloric acid is about 100 e.s.u. less than that in potassium chloride solutions at the lowest condentrations studied, and the difference rises slightly with increasing concentration. This is probably due, at least in part, to the fact that in the acid solution the dissociation of ions originally present in the conductivity water is suppressed by addition of acid, and their contribution to the total charge is lost. It is seen from Table 2 that the charge in the pure solvent (" equilibrium " water, $\kappa \simeq 1$ gemmho) is about 400 e.s.u., so we must conclude that the contribution of the " solvent charge " is not additive to the " solute charge " in the salt solution—owing to the fact that addition of solute alters the potential in the adsorbed layer (see also Dulin and Elton, 1953, *loc. cit.*). The charge in nitric acid is also less than that in potassium nitrate solutions, the difference being about 30 e.s.u. at the lowest, and about 200 e.s.u. at the highest, concentrations.

The charges in nitric acid are consistently lower than those in hydrochloric acid, the difference being 80—125 e.s.u. over the concentration range 1×10^{-5}N to 2×10^{-3}N. The charges in potassium nitrate solutions are consistently lower than those in potassium chloride solutions, the difference being 60—215 e.s.u. over this concentration range. These differences indicate that the adsorption energy of the nitrate ion at a carborundum surface is appreciably less (*i.e.*, more negative) than that of the chloride ion. This has been confirmed by measurements of ion adsorption (Elton and Mitchell, *loc. cit.*), the values for adsorption from a 10^{-3}N-solution being $-4{\cdot}0$ kcal. for the nitrate ion, and $-3{\cdot}8$ kcal. for the chloride ion.

The results for potassium hydroxide solutions were obtained in water of very low carbon dioxide content ($\kappa \simeq 0{\cdot}2$ gemmho) in order to avoid the complication of considerable reaction of the hydroxyl ion with bicarbonate ions from the solvent. There will therefore be an unusually small " solvent charge " in this case. The charges in potassium hydroxide solutions are very similar to those in potassium nitrate solutions, especially at the lower concentrations, so we may draw the qualitative conclusion that the adsorption energy of the hydroxyl ion at a carborundum surface is, at these concentrations, not very different from that of the nitrate ion.

Experimental

Materials.—Carborundum powder (700 mesh) was supplied by the Carborundum Company Ltd. It was cleaned by treatment with alcohol–nitric acid, followed by boiling aqua regia, and washed many times with conductivity water. Purification of the solutes used has been described previously (Parts I, III, and V, *locc. cit.*), except that for potassium hydroxide " AnalaR " pellets were washed with conductivity water to remove surface carbonate, and a solution made up in good-quality conductivity water ($\kappa \simeq 0{\cdot}2$ gemmho), and kept in a waxed bottle under nitrogen. The solution was standardised against potassium hydrogen phthalate, and used immediately.

Particle-sizing of Carborundum.—This was done as described in Part I. Specimens of two particle sizes were used, with limiting sedimentation velocities (u_0) of $3{\cdot}94 \times 10^{-3}$ and $5{\cdot}32 \times 10^{-3}$ cm./sec. The areas per g. (A_0) of the particles, determined as described in Part I (*loc. cit.*), were $6{\cdot}23 \times 10^4$ and $3{\cdot}85 \times 10^4$ cm.^{2}, respectively.

Sedimentation Experiments.—These were carried out in a cell of the type described in Part IV (*loc. cit.*). The cell, containing the carborundum and about 180 ml. of conductivity water, was clamped vertically in a thermostat at 25·00° ± 0·01°. Additions of electrolyte stock solution were made with a microburette, and the conductivity of the solutions obtained was measured on a conventional A.C. bridge, the concentrations being calculated from the measured conductivities. The weight of particles per ml. of the suspension (M) was determined before each run by taking 25 ml. of the original suspension in conductivity water, centrifuging out the particles, and drying and weighing them on a microbalance. (In this work M was usually between 4×10^{-5} and 4×10^{-4} g./ml.) As the volume of the suspension was changed during the run by addition of electrolyte solution, a slightly different value of M has to be used at each concentration. This technique was used in preference to the method of successive dilution in order to avoid loss of a slight film of particles which tended to cling to the surface of the solution.

BATTERSEA POLYTECHNIC, S.W.11. [*Received, July 13th,* 1953.]

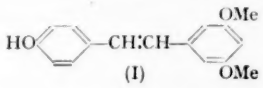
---

742. *The Chemistry of Extractives from Hardwoods. Part XIII.* Colourless Constituents of* Pterocarpus *Species.*

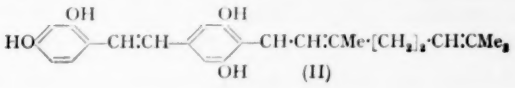
By F. E. KING, C. B. COTTERILL, D. H. GODSON, L. JURD, and T. J. KING.

An examination of the heartwood of *Pterocarpus dalbergioides*, *P. macrocarpus*, *P. soyauxii*, and *P. tinctorius* has revealed the somewhat more general occurrence of pterocarpin, homopterocarpin, and pterostilbene, compounds previously isolated from red sandalwood (*P. santalinus*), *e.g.* by McGookin, Robertson, and Whalley (*J.*, 1940 787), and Späth and Schläger (*Ber.*, 1940, **73**, 1 and 881). None of these products was detected, however, in muninga (*P. angolensis*) which is also atypical in containing angolensin (King, King, and Warwick, *J.*, 1952, 1920) and prunetin among its light petroleum-soluble constituents.

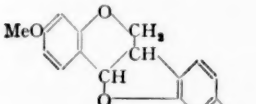
IT has become apparent with the development of chemical investigations on the woods of Gymnosperms, commonly known as softwoods, that valuable new evidence concerning their genetical relations can be elicited from a study of heartwood extractives. This is strikingly illustrated by the work of Erdtman and his collaborators who in the course of their examination of softwoods have shown, for example, that 3 : 5-dihydroxystilbene (pinosylvin) or its methyl ether is present in the heartwood of the majority of *Pinus* species but is not encountered in any other genus of coniferous trees (see chapters by H. Erdtman in "Progress in Organic Chemistry," Butterworth, 1951, edited by J. W. Cook; Wise and Jahn, "Wood Chemistry," Reinhold, 2nd edn., 1952). No comparable observations as yet exist for the innumerable dicotyledonous trees, from which are



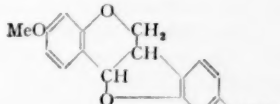
(I)



(II)



(III)



(IV)

obtained the so-called hardwoods, but the discovery of pterostilbene (I) (Späth and Schläger, *Ber.*, 1940, **73**, 881) and of chlorophorin (II) (King and Grundon, *J.*, 1949, 3348; 1950, 3547) suggests that stilbene derivatives may also prove to be characteristic of certain hardwood genera.

Pterostilbene was obtained (Späth and Schläger, *loc. cit.*) from red sandalwood (*Ptero-*

* Part XII, *J.*, 1953, 1192.

carpus santalinus), formerly used, together with other " insoluble red " woods, *e.g.*, narra-wood (*P. indicus*) and camwood (*Baphia nitida*),* for dying cotton and wool. Various earlier investigators isolated three other colourless constituents of red sandalwood, namely, pterocarpin (III), homopterocarpin (IV), and santal. The structures of (III) and (IV) were elucidated by McGookin, Robertson, and Whalley (*J.*, 1940, 787) and of santal by Robertson, Suckling, and Whalley (*J.*, 1949, 1571) using products extracted from the commercial dyewood. Späth and Schläger (*Ber.*, 1940, **73**, 1) also obtained pterocarpin and homopterocarpin and independently suggested the constitution (IV), but they alone have recorded the occurrence of pterostilbene in the wood. These somewhat divergent results may arise in part from variations in the botanical source of the raw material; it is not clear whether the identity of the specimens under investigation was definitely established.

Several well-known commercial timbers are derived from the genus *Pterocarpus*, for example, Andaman padauk (*P. dalbergioides*) and Burma padauk (*P. macrocarpus*), and the wood of the African species *P. angolensis* (muninga) is now regularly imported. From alcoholic extracts of muninga, 6 : 4'-dihydroxy-5 : 7-dimethoxy*iso*flavone (muningin) (King, King, and Warwick, *J.*, 1952, 96), 2 : 4-dihydroxyphenyl 1-*p*-methoxyphenylethyl ketone (angolensin) (*idem*, *ibid.*, p. 1920), and prunetin (King and Jurd, *J.*, 1952, 3211) were recently isolated, but there appears to have been no chemical examination of Andaman or Burma padauk. Accordingly, the products extracted by boiling light petroleum from these three timbers and from the wood of two other species, *P. soyauxii* and *P. tinctorius*, have been investigated, with results that indicate a more general occurrence of the compounds (I), (III), and (IV) within the genus. We are indebted to Mr. B. J. Rendle, D.S.I.R. Forest Products Research Laboratory, for help in procuring the wood samples and for confirmation of their identity, and to Professor A. Robertson, F.R.S., for authentic specimens of pterocarpin and homopterocarpin.

The results, which are summarised in the accompanying Table, show that pterostilbene (I) is a common constituent of four of the varieties so far examined; the fifth, *P. angolensis*, is peculiar in that none of the compounds (I), (III), and (IV) was detected in the 35 kg. of wood extracted. On the other hand, the light petroleum-soluble fraction from this species contained prunetin and comparatively large amounts of angolensin, products not observed in the corresponding extracts of the remaining woods.

Distribution of pterostilbene, pterocarpin, and homopterocarpin in the heartwood of Pterocarpus *species.*

	Pterostilbene	Pterocarpin	Homopterocarpin
P. dalbergioides	+	+	—
P. macrocarpus	+	+	—
P. soyauxii	+	—	+
P. tinctorius	+	—	—
P. angolensis	—	—	—

+ = isolated; — = not found.

Erdtman (*op. cit.*) has suggested that the presence of pinosylvin or its methyl ether is responsible for the resistance of the wood of *Pinus* species to fungus and insect attack. Experiments carried out at the D.S.I.R. Forest Products Research Laboratory show that pterostilbene is strongly toxic to the brown rot fungus *Coniophora cerebella* but not to *Polystictus versicolor* (white rot fungus); pterocarpin and homopterocarpin do not affect the growth of these wood-rotting fungi (personal communication from Dr. W. P. K. Findlay and Dr. J. G. Savory to whom the authors express their thanks). The presence of pterostilbene, therefore, in four of the above *Pterocarpus* species is at least a contributing factor to the fungus-resisting qualities of their heartwoods. The durability of muninga, on the other hand, must be attributed to other constituents, including, probably, those originally isolated by alcohol extraction, *viz.*, angolensin, muningin, and prunetin.

* The description barwood sometimes applied to this species is now restricted ("Nomenclature of Commercial Timbers," Provisional Supplement to British Standards 881 and 589, 1948) to *P. soyauxii* alternatively known as African padauk.

Except in the case of *P. tinctorius*, where the quantity of wood was limited, a plastic mass separated from the petroleum solution during the extractions, and pterocarpin or homopterocarpin, if present, crystallised from the concentrated supernatant liquid. The pterostilbene was present in the resinous deposit but all attempts to isolate it by the usual methods were unsuccessful. It was therefore remarkable to find that treatment of the resin at room temperature with acetic anhydride and a catalytic quantity of pyridine led to the immediate crystallisation of the previously unknown acetylpterostilbene. The acetate was readily oxidised by potassium permanganate, thereby affording 3 : 5-dimethoxybenzoic acid, but the accompanying *p*-acetoxybenzoic acid could not be isolated in pure condition. Ozonolysis and treatment with alkali gave, however, the readily separable 3 : 5-dimethoxy- and *p*-hydroxy-benzaldehyde. Pterostilbene was obtained from the acetate by aqueous alkaline hydrolysis and careful neutralisation with acetic acid. From it the benzoate, *p*-nitrobenzoate, and 3 : 5-dinitrobenzoate was prepared in addition to the methyl ether described by Späth and Schläger (*loc. cit.*).

In consequence of the protracted attempts to detect the colourless compounds characteristic of the other species, the light petroleum-soluble constituents of *P. angolensis* were subjected to a more detailed examination. Apart from a small percentage of steam-volatile liquid, the bulk of the extract consisted of an undistillable oil from which minute amounts of crystalline compounds were isolated as described in the Experimental section. Among those characterised were " β "-sitosterol, a previously unknown sterol $C_{29}H_{50}O$, acetyloleanolic acid, and a new triterpene, muningol $C_{30}H_{50}O$.

Experimental

With the exception of *P. tinctorius*, where the quantity of wood was limited, extractions were carried out under reflux in a metal apparatus, the coarsely powdered wood being supported by a gauze disc in a cylindrical container open at both ends and placed immediately above the surface of the boiling solvent.

Pterocarpus dalbergioides.—During the 8-hr. extraction of the wood (4·2 kg.) with boiling light petroleum (b. p. 60—80°) a pale brown plastic resin (60 g.) was deposited. Concentration of the light yellow supernatant liquid to *ca.* 200 c.c. caused separation of pterocarpin which after recrystallisation from light petroleum and from ethanol formed plates, m. p. and mixed m. p. 164·5°, $[\alpha]_D$ −214·5° (*c*, 0·53 in $CHCl_3$) (Found: C, 68·5; H, 5·2; OMe, 9·2. Calc. for $C_{17}H_{14}O_5$: C, 68·5; H, 4·7; OMe, 10·4%). With a further small quantity isolated by crystallisation of the aqueous alkali-insoluble portion of the resin, the total yield of pterocarpin was 4·8 g. (0·11%). Treatment of the resin, either before or after removal of the pterocarpin residue, with acetic anhydride–pyridine gave *acetylpterostilbene* which when completely precipitated with water and crystallised from ethanol (charcoal) formed needles (22·8 g., 0·55%), m. p. 128° (Found: C, 72·4; H, 6·5; OMe, 21·0. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·1; 2OMe, 20·8%).

Pterocarpus macrocarpus.—Extraction (8 hr.) of the wood (4 kg.) with boiling light petroleum yielded a sparingly soluble brown resin (85 g.), similar to that obtained from *P. dalbergioides*, and a pale yellow solution. The latter gave pterocarpin, m. p. and mixed m. p. 164·5° (total yield with a small quantity isolated by alkali-treatment of the resin, 4·94 g., 0·12%). Acetylation of the resin afforded acetylpterostilbene (20·4 g., 0·51%), m. p. 128°.

Pterocarpus soyauxii.—As with the foregoing species, a red brown resin (67·6 g.) separated during the extraction (8½ hr.) of 3½ kg. of the wood. The supernatant liquid was concentrated to small bulk, thereby giving a sticky solid which when crystallised from light petroleum and from ethanol gave homopterocarpin (12 g.), initially as a new dimorphic variety in stout prisms, m. p. 71°, but afterwards as needles, m. p. and mixed m. p. 87—88°, $[\alpha]_D$ −199° (*c*, 0·896 in $CHCl_3$) (Found: C, 71·7; H, 5·7; OMe, 19·7. Calc. for $C_{17}H_{16}O_4$: C, 71·8; H, 5·7; 2OMe, 21·8%). Treatment of the red-brown resin with aqueous alkali left a further amount of homopterocarpin (combined yield, 25·5 g., 0·7%). Acetylation of the alkali-soluble material gave acetylpterostilbene (6·8 g., 0·2%), m. p. 128°.

Pterocarpus tinctorius.—The powdered wood (280 g.) was heated under reflux for periods of 8 hr. with 3 successive quantities (1½ l.) of light petroleum (b. p. 60—80°). Evaporation gave a yellow oil (3 g.) which was dissolved in ether and shaken with aqueous sodium hydroxide. The light brown gum precipitated from the aqueous layer with dilute acetic acid was collected and crystallised from light petroleum (charcoal), pterostilbene (0·92 g., 0·3%) being obtained as

plates, m. p. and mixed m. p. 88—89°. Acetylation with pyridine–acetic anhydride at room temperature gave acetylpterostilbene, m. p. 128°. The alkali-insoluble portion of the extract failed to give crystalline products when seeded in light petroleum solution with pterocarpin or homopterocarpin.

Pterostilbene.—Acetylpterostilbene (3 g.) was heated with boiling 2N-aqueous sodium hydroxide (50 c.c.) until dissolved. Owing to the marked inclination of the product to polymerise under acid conditions the cooled solution was carefully neutralised with dilute acetic acid. The resulting oil slowly crystallised and separated from light petroleum in plates, m. p. 88—89°. With methyl sulphate in 2N-alkali it yielded 3 : 5 : 4′-trimethoxystilbene, prisms, m. p. 57° [from light petroleum (b. p. 40—60°)]. Späth and Schläger (*loc. cit.*) record pterostilbene, m. p. 87—88° (methyl ether, m. p. 56—57°). *Benzoylpterostilbene* crystallised from ethanol in long rectangular plates or prisms, m. p. 113—114° (Found: C, 76·5; H, 5·5; OMe, 17·7. $C_{23}H_{20}O_4$ requires C, 76·6; H, 5·6; 2OMe, 17·2%); the p-*nitrobenzoate*, golden-yellow needles from a large volume of ethanol, had m. p. 166—167° (Found: C, 67·6; H, 4·4; N, 3·1. $C_{23}H_{19}O_6N$ requires C, 68·1; H, 4·7; N, 3·5%), and the 3 : 5-*dinitrobenzoate*, long rectangular golden-yellow plates from acetic acid, had m. p. 242° (Found: C, 61·0; H, 3·8; N, 5·8. $C_{23}H_{18}O_8N_2$ requires C, 61·3; H, 4·0; N, 6·2%).

Oxidation of Acetylpterostilbene.—(a) *With potassium permanganate.* Powdered potassium permanganate (0·4 g.) was slowly added to a cold solution of acetylpterostilbene (0·2 g.) in acetone (20 c.c.). When reaction ceased, the precipitate was separated and stirred with water (25 c.c.). The filtered aqueous solution was acidified and the resulting solid collected and extracted with boiling water (10 c.c.). The acid separating from the cold solution had m. p. 154—155°, unchanged by repeated recrystallisation (*p*-acetoxybenzoic acid, m. p. 185°); the undissolved product consisted of 3 : 5-dimethoxybenzoic acid, and it crystallised from water in needles (0·03 g.), m. p. 185° (Found: C, 59·4; H, 5·8; OMe, 32·9. Calc. for $C_9H_{10}O_4$: C, 59·3; H, 5·5; 2OMe, 34·1%).

(b) *With ozone.* A solution of acetylpterostilbene (1·5 g.) was ozonised in ethyl acetate (30 c.c.), and after removal of the solvent under reduced pressure the residue was treated with water (10 c.c.) and palladised charcoal. Next day, after being heated for 5—10 min. at 100°, the solution was filtered, and the product isolated with ether was heated with 2N-sodium hydroxide, thereby being resolved into (A) alkali-soluble and (B) alkali-insoluble fractions. From (A), a 2 : 4-dinitrophenylhydrazone, red plates (from ethanol), m. p. 276°, identical with *p*-hydroxybenzaldehyde 2 : 4-dinitrophenylhydrazone, and a semicarbazone, pale yellow plates, m. p. 214°, were obtained. (B) gave a *p*-nitrophenylhydrazone, m. p. 183—185°, a semicarbazone (m. p. 174—175°) and an oxime, m. p. 115—116°, values which are in agreement with those recorded for 3 : 5-dimethoxybenzaldehyde.

Pterocarpus angolensis.—The finely powdered heartwood (3 kg.) was extracted with boiling light petroleum (b. p. 60—80°) for 20 hr. The clear solution was then decanted from the mixture of red-brown resin (40 g.) and clusters of large colourless crystals (25 g.). The latter after recrystallisation from benzene–light petroleum gave angolensin (15 g.), m. p. and mixed m. p. 117—118°; prunetin (0·5 g.), m. p. 237—238°, was deposited from a chloroform solution of the resin.

The petroleum-soluble portion (X) of the extract (40 g.) was partitioned between ether and 2N-sodium hydroxide, the latter yielding when acidified a red-brown oil (10 g.). From a solution of this oil in methanol (20 c.c.) traces of crystalline solid, m. p. 78°, first separated [Found: C, 78·2; H, 12·7%; *M* (Rast), 349], and then, after concentration to 5 c.c., acetyloleanolic acid (0·23 g.), m. p. 258°. The alkali-insoluble fraction (30 g.), an orange oil, was refluxed for 1 hr. with alcoholic potassium hydroxide (25 g. in 150 c.c.). The acidic hydrolysis product remained liquid but from its solution in methanol a further minute amount of the substance, m. p. 78° [Found: C, 78·6; H, 12·8%; *M* (Rast), 393], crystallised. A methanol solution of the neutral "hydrolysate" deposited sitosterol (0·4 g.), m. p. 136° (A). Afterwards the oil recovered from the methanol was dissolved in light petroleum, whereupon crystalline solid (0·2 g.) separated which when purified by fractionation on alumina had m. p. 252—254° (Found in sample dried at 170° *in vacuo*: C, 82·0; H, 10·7%). The remaining light petroleum solution (X) (after alkali-extraction) was also fractionated chromatographically on alumina, the residues from 3 batches (9 kg. of wood) being concentrated to 100 c.c., and the column eluted successively with light petroleum, benzene, and ether. The ether eluate contained "β"-sitosterol (0·9 g.), m. p. 133—134°, and the yellow oil obtained from the benzene solution when dissolved in acetic acid (10 c.c.) yielded muningol (0·7 g.), m. p. 107°. The bulk of the material was petroleum-soluble, of which a portion (16 g.) was steam-volatile, being obtained as a mobile yellow oil

(10 g.), b. p. 148—152°/15 mm. [Found: C, 85·3; H, 11·1%; *M* (Rast), 214]. Distillation through a Hempel column gave 2 colourless fractions: (*a*) (3 g.) which after being heated with sodium had b. p. 128—132°/12 mm., $[\alpha]_D$ +14·5°, n^{20} 1·514 [Found: C, 88·5; H, 11·8%; *M* (Rast), 207. $C_{15}H_{24}$ requires C, 88·2; H, 11·8%; *M*, 204], and (*b*) (3 g.) b. p. 132—135°/12 mm., n^{20} 1·5145, apparently containing oxygenated material not removed by sodium (Found: C, 86·7; H, 11·1%). The steam-involatile residue was a viscous gum which decomposed on attempted distillation at 0·03 mm.

Acetyloleanolic Acid.—The product of m. p. 258°, after recrystallisation from benzene–light petroleum and from methanol, formed shining needles, m. p. and mixed m. p. 264—265°, $[\alpha]_D$ +73·8° (*c*, 0·8 in $CHCl_3$) [Found: C, 76·7; H, 10·0; OAc, 9·7%; *M* (Rast), 461. Calc. for $C_{32}H_{50}O_4$: C, 77·1; H, 10·1; OAc, 9·7%; *M*, 499]. Its solution in methanol with ethereal diazomethane gave methyl acetyloleanolate, m. p. and mixed m. p. 221—223°, $[\alpha]_D$ +70·2° (*c*, 0·5 in $CHCl_3$) (Found: C, 77·3; H, 9·9. Calc. for $C_{33}H_{52}O_4$: C, 77·3; H, 10·2%). Hydrolysis of the compound of m. p. 264—265° with alcoholic potassium hydroxide yielded oleanolic acid, m. p. 303—304°.

Sitosterols.—The "β"-sitosterol, crystallised five times from methanol, had m. p. 137—138°, $[\alpha]_D$ −35° (*c*, 2·5 in $CHCl_3$); its acetate had m. p. 129—130°, $[\alpha]_D$ −41° (Found: C, 81·4; H, 11·6. Calc. for $C_{31}H_{52}O_2$: C, 81·5; H, 11·5%), and its 3 : 5-dinitrobenzoate m. p. 195—196° (Found: C, 70·8; H, 8·5. Calc. for $C_{36}H_{52}O_6N_2$: C, 71·0; H, 8·6%). The sitosterol (A), six times crystallised from methanol, had m. p. 137—138°, $[\alpha]_D$ −23° (in $CHCl_3$), and gave a deep blue Liebermann–Burchard reaction; it gave an acetate, m. p. 118—120°, $[\alpha]_D$ −21·8° (*c*, 2·6 in $CHCl_3$) (Found: C, 82·0; H, 11·4%), and a 3 : 5-dinitrobenzoate, m. p. 214° (Found: C, 71·4; H, 8·9%). From the mother-liquors of the first crystallisation of (A) obtained from 25 kg. of muninga, concentrated to 50 c.c., a crystalline solid separated. Recrystallisation from methanol yielded colourless needles of a new *sterol*, m. p. 152—153°, $[\alpha]_D$ −41° (*c*, 0·45 in $CHCl_3$) (Found, after drying at 150° *in vacuo*: C, 83·5; H, 11·6. $C_{29}H_{50}O$ requires C, 84·0; H, 12·1%). It gave a blue Liebermann–Burchard colour, and its 3 : 5-*dinitrobenzoate* crystallised from methanol–acetone in long leafy plates, m. p. 218—219° (Found: C, 70·9; H, 8·5. $C_{36}H_{52}O_6N_2$ requires C, 71·0; H, 8·6%).

Muningol.—This was obtained as plates, m. p. 107°, from acetic acid, and from methanol as needles, m. p. 97° raised by drying at 100° to 107—108°, $[\alpha]_D$ +44·2° (*c*, 3·7 in $CHCl_3$) (Found: after drying above the m. p. *in vacuo*: C, 84·1; H, 11·7. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%); the p-*nitrobenzoate* had m. p. 217° (Found: C, 77·0; H, 9·4; N, 2·4. $C_{37}H_{53}O_4N$ requires C, 77·2; H, 9·3; N, 2·4%); the 3 : 5-*dinitrobenzoate* had m. p. 185—186° (Found: C, 71·9; H, 8·6; N, 4·5. $C_{37}H_{52}O_6N_2$ requires C, 71·6; H, 7·4; N, 4·5%). An acetate, m. p. 116°, and a benzoate, m. p. 127°, were also prepared.

A solution of muningol (31·5 mg.) in acetic acid (10 c.c.) with palladium–charcoal catalyst absorbed 1·75 c.c. of hydrogen at N.T.P. (theor. for 1 double bond, 1·68 c.c.). The product, *dihydromuningol*, crystallised from methanol in needles, m. p. (after drying at N.T.P.) 106—107°, and 103—104° when mixed with muningol (Found: after drying above the m. p. *in vacuo*: C, 84·1; H, 12·1. $C_{30}H_{52}O$ requires C, 84·0; H, 12·2%); it gave a p-*nitrobenzoate*, m. p. 220—221° (Found: C, 76·7; H, 9·6. $C_{37}H_{55}O_4N$ requires C, 76·9; H, 9·6%), and a 3 : 5-*dinitrobenzoate*, m. p. 187—188° (Found: C, 71·1; H, 8·7; N, 4·3. $C_{37}H_{54}O_6N_2$ requires C, 71·35; H, 8·7; N, 4·5%). The acetate had m. p. 128°.

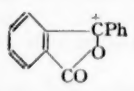
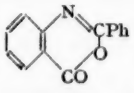
Two of the authors (C. B. C., D. H. G.) thank the Department of Scientific and Industrial Research for the award of maintenance allowances.

THE UNIVERSITY, NOTTINGHAM. [*Received, July 28th*, 1953.]

743. *The Mechanism of the Schmidt Reaction with o-Benzoylbenzoic Acid.*

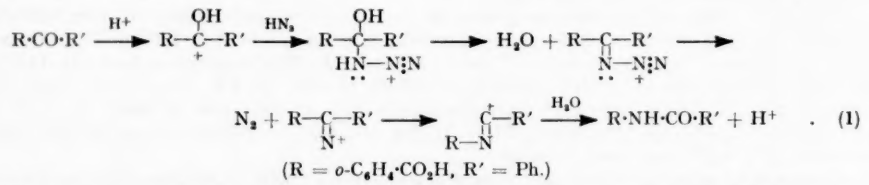
By C. L. Arcus and M. M. Coombs.

The interaction of *o*-benzoylbenzoic acid with hydrazoic and sulphuric acids yields 6-oxo-2-phenyl-4 : 5-benz-1 : 3-oxazine (II); *N*-benzoylanthranilic acid (Badger, Howard, and Simons, *J.*, 1952, 2849) arises from a subsequent hydrolysis. A mechanism for the reaction is proposed in which the oxazine is formed by ring-expansion from the cyclic cation (I).

(I)   (II)

2-*p*-Toluoylbenzoic acid, by a similar reaction, yields 6-oxo-2-*p*-tolyl-4 : 5-benz-1 : 3-oxazine.

Badger, Howard, and Simons (*J.*, 1952, 2849) have allowed *o*-benzoylbenzoic acid in solution in trichloroacetic acid, and also in chloroform, to react with hydrazoic acid in the presence of sulphuric acid: the reaction mixtures were finally poured into water. From the reaction in trichloroacetic acid there was obtained *N*-benzoylanthranilic acid (91%); reaction in chloroform gave this acid and 6-oxo-2-phenyl-4 : 5-benz-1 : 3-oxazine (II) in 31% and 67% yield respectively. These authors envisage the reaction as that of a substituted benzophenone, and have adopted (and slightly modified) a mechanism which Smith and his co-workers (*J. Amer. Chem. Soc.*, 1948, **70**, 320; 1950, **72**, 2503, 3718) have proposed for ketones:



(R = *o*-C_6H_4·CO_2H, R′ = Ph.)

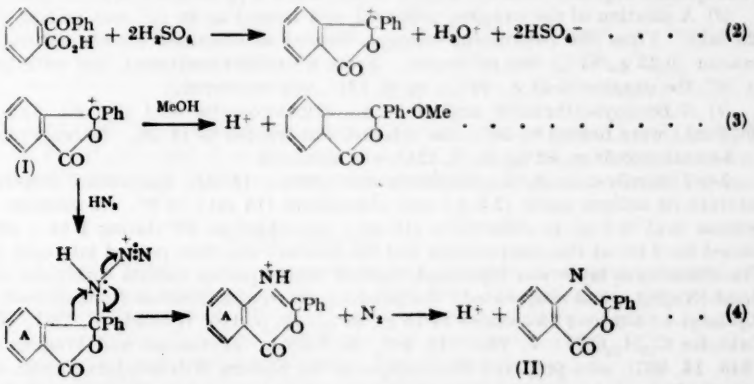
We have repeated the reaction using the trichloroacetic acid method of Badger *et al.*, and obtained *N*-benzoylanthranilic acid (78%); by a modified procedure using chloroform as solvent the oxazine was obtained in 80% yield. The following facts relating to the reaction have been ascertained:

The oxazine, when its solution in trichloroacetic–sulphuric acid is diluted with water, becomes largely hydrolysed to *N*-benzoylanthranilic acid. If the acid solution is diluted with chloroform and the mixture shaken with cold water, the oxazine can be recovered nearly quantitatively and, when the acidic solution from the Schmidt reaction in trichloroacetic acid is similarly treated, the oxazine (91%) is obtained. The oxazine is thus the actual product of the interaction of *o*-benzoylbenzoic acid with hydrazoic–sulphuric acid in both trichloroacetic acid and chloroform.

N-Benzoylanthranilic acid, in either chloroform or trichloroacetic acid, undergoes ring closure when treated with sulphuric acid, as in the Schmidt reaction procedure; the oxazine can be isolated in good yield from the former solvent, and also from the latter provided that chloroform is added as a diluent.

Newman, Kuivila, and Garrett (*ibid.*, 1945, **67**, 704) have found that *o*-benzoylbenzoic acid in solution in sulphuric acid has a van't Hoff *i* factor of 3·8, in agreement with ionisation according to equation (2), which requires $i = 4$. Further evidence for the cyclic structure of the cation is provided by the observation (Newman, *ibid.*, 1942, **64**, 2324) that considerable methyl *pseudo*-*o*-benzoylbenzoate is formed (reaction 3) when a solution of *o*-benzoylbenzoic acid in sulphuric acid is poured into methanol.

It is now suggested that 6-oxo-2-phenyl-4 : 5-benz-1 : 3-oxazine arises from the interaction of the cation (I) with hydrazoic acid, followed by a ring-expansion (4), closely analagous to that occurring during the formation of phenanthridine by the reaction of



hydrazoic–sulphuric acid with fluoren-9-ol (Arcus and Mesley, *J.*, 1953, 178). The four electrons initially present as the A–CPh bond and the nitrogen lone-pair appear finally as the A–$\overset{+}{N}$H bond and the π-electrons of the $\overset{+}{N}$H=CPh bond.

It has been found (above) that *N*-benzoylanthranilic acid is converted into the oxazine under the conditions of the Schmidt reaction in either chloroform or trichloroacetic acid, whence the possibility cannot be excluded that reaction proceeds by mechanism (1), followed by ring closure of the acid. However, in view of the evidence of Newman *et al.* for the cyclic structure of the cation, it is concluded that mechanism (3) (which results directly in the oxazine) is the more probable.

The migratory aptitudes shown by different groups during the Schmidt reaction of ketones have been studied by Badger and Smith and their co-workers (*locc. cit.*) and by Westland and McEwen (*J. Amer. Chem. Soc.*, 1952, **74**, 6141); mechanism (4) implies that the migratory aptitude of the *o*-carboxyphenyl group cannot properly be compared with the aptitudes of groups which do not interact with the carbonyl group.

2-*p*-Toluoylbenzoic acid (in solution in chloroform) reacted with hydrazoic–sulphuric acid to yield 6-oxo-2-*p*-tolyl-4 : 5-benz-1 : 3-oxazine.

Experimental

The Schmidt Reaction.—*o-Benzoylbenzoic acid.* Badger, Howard, and Simons (*loc. cit.*) refer to their procedure with trichloroacetic acid as method *B*, and to that with chloroform as method *A*; these designations have been retained.

o-Benzoylbenzoic acid (4·52 g.) yielded, by method *B*, *N*-benzoylanthranilic acid (3·75 g., 78%), m. p. 176—178°. This reaction was repeated, but the acidic solution was poured into chloroform (200 ml.). The chloroform solution was washed with water and with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated. 6-Oxo-2-phenyl-4 : 5-benz-1 : 3-oxazine (4·05 g., 91%), m. p. 120°, was obtained; after recrystallisation from ethanol, it (2·8 g.) had m. p. 123°.

o-Benzoylbenzoic acid (4·52 g.), subjected to the Schmidt reaction by the method (*A'*) described below for 2-*p*-toluoylbenzoic acid, yielded 6-oxo-2-phenyl-4 : 5-benz-1 : 3-oxazine (3·55 g., 80%), m. p. 122·5° (Found: C, 75·5; H, 4·4; N, 6·3. Calc. for $C_{14}H_9O_2N$: C, 75·3; H, 4·1; N, 6·3%).

Hydrolysis and Ring Closure.—(*a*) 6-Oxo-2-phenyl-4 : 5-benz-1 : 3-oxazine (3·05 g.) gave, by method *B* (sodium azide omitted), *N*-benzoylanthranilic acid (3·05 g., 93%), m. p. 177°.

(*b*) *N*-Benzoylanthranilic acid (2·25 g.) yielded, by method *A'* (sodium azide omitted), 6-oxo-2-phenyl-4 : 5-benz-1 : 3-oxazine (1·85 g., 89%), m. p. 123°.

(*c*) The oxazine (0·30 g.) was heated with trichloroacetic acid (2·0 g.) and sulphuric acid (0·8 ml.) for 1 min. to 50° and the solution was poured into water. The precipitate was filtered

off, washed, and dried; it yielded *N*-benzoylanthranilic acid (0·26 g., 80%), m. p. 177°. A similar experiment, but with heating for 4 hr. at 50°, gave *N*-benzoylanthranilic acid (0·20 g., 62%), m. p. 178°. The oxazine was recovered unchanged after it had been kept overnight in a refrigerator together with the diluted mixed acids, a process which forms part of procedure *B*.

(*d*) A solution of the oxazine, prepared and heated as in (*c*), was poured into chloroform (25 ml.). From the chloroform solution, treated as described for the Schmidt reaction, the oxazine (0·25 g., 83%) was recovered. From a similar experiment, but with heating for 4 hr. at 50°, the oxazine (0·28 g., 93%), m. p. 121°, was recovered.

(*e*) *N*-Benzoylanthranilic acid (0·50 g.), trichloroacetic acid (4·0 g.), and sulphuric acid (0·75 ml.) were heated to 50°; the solution was treated as in (*d*). 6-Oxo-2-phenyl-4 : 5-benz-1 : 3-oxazine (0·38 g., 82%), m. p. 121°, was obtained.

2-p-*Toluoylbenzoic Acid.*—Sulphuric acid (98%; 15 ml.) was added dropwise to a stirred mixture of sodium azide (2·6 g.) and chloroform (15 ml.) at 0°. A solution of 2-*p*-toluoylbenzoic acid (4·8 g.) in chloroform (15 ml.) was added at 30° during 1 hr.; stirring was continued for 2 hr. at this temperature and the mixture was then poured into cold water (250 ml.). The chloroform layer was separated, washed with aqueous sodium carbonate and with water, dried (Na_2SO_4), and evaporated; the product, on recrystallisation from ethanol, yielded 6-oxo-2-*p*-tolyl-4 : 5-benz-1 : 3-oxazine (4·15 g., 88%), m. p. 155° (Found: C, 76·1; H, 4·7; N, 6·1. Calc. for $C_{15}H_{11}O_2N$: C, 76·0; H, 4·7; N, 5·9%). Zentmeyer and Wagner (*J. Org. Chem.*, 1949, **14**, 967), who prepared this compound by heating *N*-toluoylanthranilic acid with acetic anhydride, record m. p. 154·5°.

Thanks are expressed to the Government Grants Committee of the Royal Society and to Imperial Chemical Industries Limited, for grants.

Battersea Polytechnic, London, S.W.11. [*Received, August 8th*, 1953.]

---

744. *Cinnolines. Part XXXII.* Further Experiments on the Effects of Heterocyclic Nuclei as Substituents in the Widman–Stoermer Synthesis.*

By A. J. Nunn and K. Schofield.

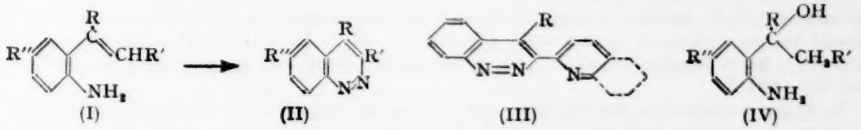
A number of 4-aryl-3-pyridyl- and -quinolyl-cinnolines have been synthesised by the Widman–Stoermer method. A *p*-methoxyphenyl group at the potential cinnoline $C_{(4)}$-position renders cinnoline formation very rapid and independent of pH, provided the latter is not so high as to endanger the stability of the diazonium salt. In contrast the formation of 4-phenyl-3-pyridyl- and -quinolyl-cinnoline depends considerably on the pH, and yields decrease rapidly with increasing acid concentration. In the diazotisation of 1-*o*-aminophenyl-1-phenyl-2-2′-quinolylethylene in hydrochloric acid, but not in sulphuric acid, it is possible that the Pschorr cyclisation competes with cinnoline formation.

Related observations on the preparation of 4-heteroarylcinnolines are described.

It was shown earlier (Schofield, *J.*, 1949, 2408) that the ethylenes (I; R = C_6H_4·OMe-*p*, R″ = H, R′ = 2-C_5H_4N and 2-C_9H_6N) gave on diazotisation high yields of 4-*p*-methoxyphenyl-3-2′-pyridyl- and -3-2′-quinolyl-cinnoline (as II) respectively. In contrast (I; R = Ph; R′ = 2-C_5H_4N, R″ = H) gave only a poor yield of 4-phenyl-3-2′-pyridylcinnoline (as picrate), whilst (I; R = Ph; R′ = 2-C_9H_6N, R″ = H) gave tars. Similarly, (I; R = 2-C_5H_4N, R′ = R″ = H) provided a poor yield of 4-2′-pyridylcinnoline. It was suggested that ethylenes of the type (I), containing basic heterocyclic substituents, offered an interesting means of studying the effect of pH on the Widman–Stoermer synthesis. Further, the cinnolines produced would be of interest in themselves, being related (cf. III) on the one hand to numerous substances such as the phenanthrolines which are capable of chelating with metals, and on the other to pyridylquinolines possessing spasmolytic pro-

* Part XXXI, *J.*, 1953, 1811.

perties (Coates, Cook, Heilbron, Hey, Lambert, and Lewis, *J.*, 1943, 401). For these reasons we have extended the earlier work.



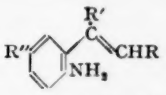
Recently (*J.*, 1952, 589) we described a number of alcohols of the types (IV; R = Aryl, R' = 2-C_5H_4N or 2-C_9H_6N; and R = 2-, 3-, and 4-C_5H_4N), and these have now been dehydrated to the ethylenes (I). The ethylenes were diazotised under a variety of conditions.

Experimental

Unless described in the present paper the alcohols and ethylenes used were prepared by Schofield (*loc. cit.*) or Nunn and Schofield (*loc. cit.*; *J.*, 1953, 716). Diazotisations were effected at 0° with aqueous sodium nitrite (5%). Ethereal extracts were dried with anhydrous Na_2SO_4.

Ethylenes.—The appropriate alcohol and sulphuric acid were heated at 95°. The solution was basified and the product was isolated with ether. Details are tabulated.

4-Aryl-3-heteroarylcinnolines.—(1) 4-p-*Methoxyphenyl-3-2'-pyridylcinnoline.* (*a*) The appropriate ethylene was diazotised in 2N-hydrochloric acid, and the solution was immediately made up to 100 c.c. with hydrochloric acid of various concentrations. Diazonium tests were negative after about 10 min. After 4 days at room temperature the solutions were neutralised with sodium carbonate and the precipitate was recrystallised from methanol until the m. p. was that of the pure cinnoline (157—158°). In each case the yield of crude cinnoline, m. p. 154—156°, was quantitative.



	Alcohol, g.	H_2SO_4 Concn.	H_2SO_4 c.c.	Time, hr.	Ethylene (I), g.
R = 2-C_5H_4N; R' = *p*-C_6H_4Me; R'' = H	2	50% v/v	32	1	2 [1]
R = 2-C_9H_6N; R' = *p*-C_6H_4Me; R'' = H	0·5	,,	8	0·5	0·5 [2]
R = 2-C_5H_4N; R' = Ph; R'' = Cl	2	Conc.	,,	,,	1·9 [1]
R = 2-C_9H_6N; R' = Ph; R'' = Cl	1	,,	4	1	0·89 [3]
R = 3-C_5H_4N; R' = *p*-MeO·C_6H_4; R'' = H	0·5	20% v/v	10	,,	0·48 [1]
R = Me; R' = 2-C_5H_4N; R'' = H	2	Conc.	8	0·5	1·84 [1]
R = R'' = H; R' = 3-C_5H_4N	,,	,,	,,	0·75	1·94 [4]
R = Me; R' = 3-C_5H_4N; R'' = H	,,	,,	,,	0·5	1·72 [1]
R = R'' = H; R' = 4-C_5H_4N	0·24	,,	1	,,	0·22 [1]
R = R'' = H; R' = 2-C_4H_3S	0·5	20% v/v	10	1	0·48 [1]

[1] Yellow oil. [2] Yellow prisms, m. p. 161—162° (Found: C, 84·9; H, 5·6. $C_{24}H_{20}N_2$ requires C, 85·7; H, 6·0%), from ethanol. [3] Yellow prisms, m. p. 147—148° (Found: C, 76·6; H, 4·7. $C_{23}H_{17}N_2Cl$ requires C, 77·4; H, 4·8%), from aqueous ethanol. [4] The ethylene was a yellow oil. Its *picrate* formed yellow needles, m. p. 125—126° (Found: C, 52·9; H, 3·8. $C_{13}H_{12}N_2,C_6H_3O_7N_3$ requires C, 53·6; H, 3·6%), from aqueous methanol.

(*b*) With the same ethylene the diazotisation was effected in acid of various concentrations. The crude products (88—91%) had m. p. 155—158°. Careful repetition of the diazotisation under the original conditions (Schofield, *loc. cit.*) realised a yield of 80·1% of the cinnoline.

(2) 4-p-*Methoxyphenyl-3-2'-quinolylcinnoline.* The diazotisations were carried out as in (*b*) above (see Table). Diazonium ions could no longer be detected after about 45 min. The products tabulated below had the m. p. (151—152°) of pure 4-*p*-methoxyphenyl-3-2'-quinolylcinnoline (Schofield, *loc. cit.*), except for the first (m. p. 144—148°), and the last (m. p. 157—158°) which appeared to be a polymorphic form (yellow needles instead of the usual plates; mixed m. p. 150—152°).

(3) *4-Phenyl-3-2'-pyridylcinnoline.* The corresponding amine was diazotised by method (*b*) above (see Table). Yields are not quoted since the products were not crystallised. The first had m. p. 141—143°, and the second, 118—120°. In a further experiment the ethylene (6 g.) was diazotised in hydrochloric acid (0·2N; 250 c.c.). After 5 days at room temperature basification gave a solid (4·25 g.; m. p. 139—141°). Passage in benzene over alumina provided

pale yellow crystals of **4-*phenyl*-3-2′-*pyridylcinnoline***, m. p. 145—146° (Found: C, 79·8; H, 4·5. $C_{19}H_{13}N_3$ requires C, 80·5; H, 4·6%).

(4) **4-*Phenyl*-3-2′-*quinolylcinnoline***. In the experiments tabulated the appropriate amine was diazotised in sulphuric acid of various concentrations. **4-*Phenyl*-3-2′-*quinolylcinnoline*** formed yellow prisms, m. p. **162—163°** (Found: C, 83·4; H, 4·8. $C_{23}H_{15}N_3$ requires C, 82·9; H, 4·5%), from aqueous ethanol. The products tabulated had m. p.s 157—160°, 152—154° and 162—163°.

In other experiments the ethylene (0·5 g.) was diazotised in hydrochloric acid of various concentrations (25 c.c. total volume), and after 3 weeks at room temperature the solutions were

Cinnoline	Wt. of ethylene (g.)	Normality of acid [1]	Approx. time after which coupling ceased	Product (g.)
1(*a*)	1·92	0·2	10 min.	1·67
	1·81	0·4	,,	1·54
	1·88	2·0	,,	1·58
	,,	5·0	,,	1·63
	1·91	9—10	,,	1·43
1(*b*)	1·96	0·2	10—15 min.	1·43
	,,	2·0	15 min.	1·49
	,,	5·0	20 ,,	,,
	1·98	8·0	25 ,,	1·51
	,,	11—12	30 ,,	1·49
2	0·5	0·2	—	0·25
	,,	2·0	—	0·38
	,,	0·5	—	0·44
	,,	8·0	—	,,
	,,	11—12	—	0·42
3	0·25	0·2	20 hr.	—
	,,	0·4	,,	—
	,,	5·0	—	Tar
	,,	8·0	5 days	,,
4	0·5	0·2	21 days	0·18
	3·0	0·4	,,	0·15
	0·5	1·0	,,	0·01

[1] The total volume of acid in experiments (1*a*) and (1*b*) was always 100 c.c., in experiments (2) 25 c.c., in (3) 12 c.c., and in (4) 25, 150, and 25 c.c.

processed as usual. The mixtures obtained were treated with picric acid in ethanol with the following results (acid concn., colour of picrates, m. p.): 0·2N, orange-yellow, 157—162°; 2N, orange-yellow, 157—162°; 5N, red, 157—162°; 8N, pale yellow, 192—195°. The first mixture yielded as the more soluble component a ***picrate*** which formed red needles, m. p. 94—95° (Found: C, 65·1; H, 3·7; N, 11·6. $C_{23}H_{15}N,C_6H_3O_7N_3$ requires C, 65·2; H, 3·4; N, 10·5%), from ethanol. [1 : 1-Diphenyl-2-2′-quinolylethylene (Ziegler and Zeiser, *Annalen*, 1931, **485**, 174) gave a *picrate* which crystallised from methanol as yellow plates, m. p. 215—216° (Found: C, 64·4; H, 3·6; N, 10·2. $C_{23}H_{17}N,C_6H_3O_7N_3$ requires C, 64·9; H, 3·8; N, 10·4%).] The fourth product (0·45 g.) was slightly impure **4-*phenyl*-3-2′-*quinolylcinnoline picrate***, which on recrystallisation from ethanol gave yellow prisms, m. p. 219—220° (Found: C, 62·0; H, 3·2; N, 14·7. $C_{23}H_{15}N_3,C_6H_3O_7N_3$ requires C, 61·9; H, 3·2; N, 14·9%).

3-2′-*Pyridyl*-4-p-*tolylcinnoline*. The ethylene (2 g.) was diazotised in 2N-hydrochloric acid (84 c.c.), and after 11 days at room temperature the product was isolated as usual. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave substantially pure material (1·5 g.; m. p. 164—165°), but this was green. Passage in benzene over alumina gave **3-2′-*pyridyl*-4-p-*tolylcinnoline***, m. p. **164—165°** (Found: C, 80·3; H, 5·4. $C_{20}H_{15}N_3$ requires C, 80·8; H, 5·1%), which formed yellow needles from aqueous ethanol.

3-2′-*Quinolyl*-4-p-*tolylcinnoline*. Diazotisation of the ethylene (0·25 g.) in hydrochloric acid (2N; 8 c.c.) gave in the usual way after 11 days a ***product*** which, crystallised from aqueous ethanol and benzene–ligroin (b. p. 60—80°), formed yellow needles (0·19 g.), m. p. 153—154° (Found: C, 82·6; H, 4·6. $C_{24}H_{17}N_3$ requires C, 82·95; H, 4·9%).

6-*Chloro*-4-*phenyl*-3-2′-*pyridylcinnoline*. The ethylene (1·9 g.) was diazotised in 0·4N-hydrochloric acid (84 c.c.). The ***product*** isolated after 15 days gave yellow prisms (1·05 g.), m. p. 143—144° (from aqueous ethanol) (Found: C, 71·7; H, 3·9. $C_{19}H_{12}N_3Cl$ requires C, 71·8; H, 3·8%).

6-*Chloro*-4-*phenyl*-3-2′-*quinolylcinnoline*. The ethylene (0·25 g.) was diazotised in 2N-

sulphuric acid (8 c.c.), and gave after 6 weeks a *product* which on crystallisation from ethanol formed yellow needles (0·12 g.), m. p. 205—206° (Found: C, 74·4; H, 3·9. $C_{23}H_{14}N_3Cl$ requires C, 75·1; H, 3·8%). No product could be isolated from an experiment in 2N-hydrochloric acid.

4-p-*Methoxyphenyl*-3-3′-*pyridylcinnoline*. A diazonium solution from the ethylene (0·48 g.) and 2N-hydrochloric acid (20 c.c.) gave after 1 hour a solid which formed yellow needles (0·37 g.) of 4-p-*methoxyphenyl*-3-3′-*pyridylcinnoline*, m. p. 145—146° (Found: C, 76·5; H, 4·7. $C_{20}H_{15}ON_3$ requires C, 76·7; H, 4·8%), from aqueous ethanol.

4-*Heteroarylcinnolines*.—4-2′-*Pyridylcinnoline*. The ethylene (0·5 g.) was diazotised in 2N-hydrochloric acid (25 c.c.). The product, obtained by the usual method, was treated with picric acid in methanol. Recrystallisation from this solvent gave the picrate (0·43 g.), m. p. 196—199° (pure m. p. 201—203°; Schofield, *loc. cit.*), from which, by treatment with alkali and ether, was isolated the cinnoline (0·18 g.), m. p. 125—126°. The results of similar experiments in acid of different concentrations are recorded below.

3-*Methyl*-4-2′-*pyridylcinnoline*. The ethylene (0·22 g.), when diazotised in 0·2N-sulphuric acid (10 c.c.), gave after 4 days a product which from benzene–ligroin (b. p. 60—80°) provided pale yellow prisms (0·1 g.) of 3-*methyl*-4-2′-*pyridylcinnoline*, m. p. 155—156° (Found: C, 75·7; H, 5·0. $C_{14}H_{11}N_3$ requires C, 76·0; H, 5·0%). Experiments with N-sulphuric gave only tars.

4-3′-*Pyridylcinnoline*. In the usual way the ethylene (1·94 g.) in 0·4N-hydrochloric acid (84 c.c.) gave a solid after 11 days. This formed from benzene–light petroleum (b. p. 60—80°) yellow needles (0·95 g.) of 4-3′-*pyridylcinnoline*, m. p. 141—142° (Found: C, 75·5; H, 4·4; N, 20·4. $C_{13}H_9N_3$ requires C, 75·3; H, 4·4; N, 20·3%).

3-*Methyl*-4-3′-*pyridylcinnoline*. The appropriate amine (1·72 g.) in 0·2N-sulphuric acid (60 c.c.) gave, as above, a *product* (1·4 g., m. p. 192—193°) which formed yellow prisms (0·88 g.), m. p. 192—193° (from ethanol) (Found: C, 75·7; H, 4·9%).

4-4′-*Pyridylcinnoline picrate*. A black tar was isolated after 6 days from the diazotisation of 1-*o*-aminophenyl-1-4′-pyridylethylene (0·22 g.) in 2N-hydrochloric acid (10 c.c.). Treatment of the tar with ethanolic picric acid gave 4-4′-*pyridylcinnoline picrate* (0·1 g.), which formed yellow prisms, m. p. 276—278° (Found: C, 51·2; H, 2·95. $C_{13}H_9N_3,C_6H_3O_7N_3$ requires C, 52·3; H, 2·8%), from methanol.

4-2′-*Thienylcinnoline*. The ethylene (0·4 g.) in 0·4N-hydrochloric acid (21 c.c.) gave after 4 days a solid which was extracted with boiling ether. From the ether yellow prisms of 4-2′-*thienylcinnoline* (0·2 g.), m. p. 85—86° (Found: C, 67·4; H, 4·0; N, 13·2. $C_{12}H_8N_2S$ requires C, 67·9; H, 3·8; N, 13·2%), were obtained.

Miscellaneous Experiments.—4-p-*Hydroxyphenyl*-3-2′-*pyridylcinnoline*. 4-*p*-Methoxyphenyl-3-2′-pyridylcinnoline (1 g.) and hydrobromic acid (8 c.c.; *d* 1·5) were refluxed for 1 hr. and the cooled solution was basified. The product (0·86 g.) gave yellow prisms of 4-p-*hydroxyphenyl*-3-2′-*pyridylcinnoline*, m. p. 265—266° (Found: C, 76·1; H, 4·1. $C_{19}H_{13}ON_3$ requires C, 76·2; H, 4·4%), from ethanol.

Diazotisation of 2-o-*aminophenyl*-3-2′-*pyridylpropylene*. The alcohol gave in the usual way with concentrated sulphuric acid a yellow oil, which formed a *dipicrate*, yellow prisms, m. p. 174—175° (from methanol) [Found: C, 45·6; N, 2·9; N, 17·0. $C_{14}H_{14}N_2,(C_6H_3O_7N_3)_2$ requires C, 46·7; H, 3·0; N, 16·8%]. Diazotisation of the ethylene in sulphuric acid of various concentrations gave tars, but with 0·2N-acid traces of yellow crystals, m. p. 149—151°, were isolated

Experiments with 1-O-*aminophenyl*-1-p-*methoxyphenyl*-2-2′-*pyridylethylene*. When the ethylene was diazotised in hydrochloric acid (0·2N), and the solution was added immediately to sodium acetate, water, and copper powder, or to aqueous dimethylamine and sodium carbonate, only diminished yields of 4-*p*-methoxyphenyl-3-2′-pyridylcinnoline resulted. When the ethylene (1·85 g.) was rapidly diazotised in 2N-hydrochloric acid (40 c.c.) and copper powder (0·5 g.) was added immediately, shaking and warming then precipitated a green solid (2·48 g.), whilst much nitrogen was evolved. Recrystallisation of the solid from ethanol gave green prisms of a *complex*, m. p. 222—223° (Found: C, 53·8; H, 3·5. $C_{20}H_{15}ON_2Cl_2Cu$ requires C, 53·65; H, 3·4%). Boiled with aqueous ammonia (*d* 0·88) the solid liberated 4-*p*-methoxyphenyl-3-2′-pyridylcinnoline.

Reaction of 4-*methylcinnoline with* p-*nitrosodimethylaniline*. 4-Methylcinnoline (4 g.), *p*-nitrosodimethylaniline (8 g.), anhydrous sodium carbonate (0·5 g.), and ethanol (270 c.c.) were refluxed for 7 hr. Filtration and concentration gave the *anil* (2·2 g.) which formed red leaflets, m. p. 196—197° (Found: C, 73·3; H, 6·1; N, 21·2. $C_{17}H_{16}N_4$ requires C, 73·9; H, 5·8; N, 20·3%), from ethanol. The anil was not hydrolysed by 40% hydrochloric acid.

1-o-*Methoxyphenyl*-1-*phenyl*-2-2′-*quinolylethylene*. *o*-Methoxybenzophenone (3 g.) in ether

(50 c.c.) was added dropwise during 10 min. to 2-quinolylmethyl-lithium [from quinaldine (6·1 g.)] in ether (100 c.c.). The mixture was refluxed for 1 hr. and then stirred for 4 hr. at room temperature. In the usual way the product was isolated as a brown oil which crystallised when rubbed with ether. The solid (3·4 g.) when crystallised from ether or aqueous methanol gave solvated prisms, m. p. 104—106° (with bubbling, after preliminary softening), which upon being dried (60°/0·5 mm.) provided prisms of 1-*o*-*methoxyphenyl*-1-*phenyl*-2-*quinolylethanol*, m.p. 122·5—123·5° (Found : C, 81·0; H, 5·8; N, 4·0. $C_{24}H_{21}O_2N$ requires C, 81·1; H, 5·9; N, 3·9%). This (0·2 g.), when heated for 2 hr. at 95° with 20% sulphuric acid (5 c.c.), gave a suspension of yellow needles. Basification and ether-extraction yielded the ethylene as a crisp froth (0·18 g.). The *picrate* formed thin yellow prisms, m. p. 209—211° (after subliming slightly at 197°) (Found : C, 63·9; H, 4·2; N, 9·7. $C_{24}H_{19}ON,C_6H_3O_7N_3$ requires C, 63·6; H, 3·9; N, 9·9%), from ethanol.

Discussion

The main results of the above experiments are tabulated below. Clearly, the cyclisation of diazotised 1-*o*-aminophenyl-1-*p*-methoxyphenyl-2-2′-pyridyl- and -2-2′-quinolyl-ethylene to the corresponding cinnolines proceeds efficiently regardless of pH except that in the second case there is a decrease in yield in very dilute acid, where presumably the stability of the diazonium salt is endangered. These results are readily understood in terms of the following representation of the reaction (V ⟶ VI ⟶ VII). Although the electron demand of the pyridyl and quinolyl groups must increase with acid concentration, the *p*-methoxyphenyl group is so powerfully electron-releasing that it is able over the whole pH range examined to satisfy the electronic demands of the Widman–Stoermer reaction (*a* and *b* in V), as well as of the pyridinium and quinolinium groups (*c*). The velocities of these cyclisations are high, and greatly exceed those in cases where R in (V) is other than methoxyl. [If 1-*o*-aminophenyl-1-*p*-methoxyphenyl-2-2′-pyridylethylene possessed the *cis*-configuration it might have been possible to convert in into (VIII), but a number of experiments with this aim gave only the cinnoline, so rapid was the cyclisation.] Data on the formation of 3-2′-pyridyl- and 3-2′-quinolyl-4-*p*-tolylcinnoline are limited but, so far as they go, consistent with what is said above. The yields are lower than with the methoxyl compounds, presumably because the slower cyclisation gives greater opportunities for alternative decompositions of the diazonium salts to occur.

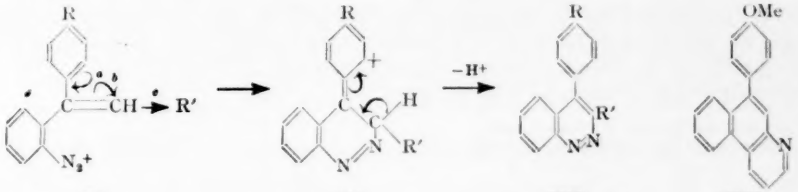
	Yield (%) in hydrochloric acid					
Cinnoline	0·2N	0·4N	N	2N	5N	8N
4-*p*-Methoxyphenyl-3-2′-pyridyl-	83·9	81·9	—	81·0	81·7	80·1
4-*p*-Methoxyphenyl-3-2′-quinolyl-	48·0	—	—	73·0	85·0	85·0
3-2′-Pyridyl-4-*p*-tolyl-	—	—	—	72·2	—	—
3-2′-Quinolyl-4-*p*-tolyl-	—	—	—	60·0	—	—
4-Phenyl-3-2′-pyridyl-	49·7	←		Tars		→
4-Phenyl-3-2′-quinolyl-	34·9 *	5·0 *	1·9 *	—	—	—
6-Chloro-4-phenyl-3-2′-pyridyl-	—	53·3	—	—	—	—
6-Chloro-4-phenyl-3-2′-quinolyl-	—	46·6 *	—	—	—	—
4-*p*-Methoxyphenyl-3-3′-pyridyl-	—	—	—	74·0	—	—
4-2′-Pyridyl-	2·5	—	16·1 *	34·1	Tar	—
3-Methyl-4-2′-pyridyl-	43·2 *	—	—	Tar	—	—
4-3′-Pyridyl-	—	46·0	—	—	—	—
3-Methyl-4-3′-pyridyl-	77·3 *	Tar	—	Tar	—	—
4-4′-Pyridyl-	—	—	—	20·4	—	—

* Experiments in sulphuric acid.

The diazotisation of 1-*o*-aminophenyl-1-phenyl-2-2′-quinolylethylene in hydrochloric acid is complicated, and is discussed below. However, the same reaction in sulphuric acid, and the diazotisations of 1-*o*-aminophenyl-1-phenyl-2-2′-pyridylethylene (in hydrochloric acid) show the expected features. Except in the most dilute acid the cinnolines could not be isolated, tars being formed. Even in dilute acid the yields were low, and the reactions were slow. These examples are in great contrast to the almost instantaneous formation of 3 : 4-diphenylcinnoline from 1-*o*-aminophenyl-1 : 2-diphenylethylene (Simpson, *J.*, 1943, 447), where the discouraging effect of the basic heterocyclic nucleus is absent. The presence of a chlorine atom, in two examples tabulated above, appears to benefit the cyclisation, perhaps because it stabilises the diazonium group, so compensating for the slow cyclisation.

It appears unlikely that 4-methyl-3-2′-pyridylcinnoline could be obtained from 2-*o*-aminophenyl-3-2′-pyridylpropylene in any circumstances.

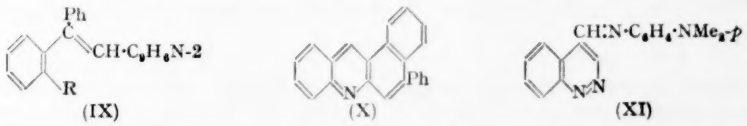
In the formation of 4-pyridylcinnolines it would be expected that a 3-pyridyl group at the potential cinnoline $C_{(4)}$-position would retard the cyclisation less than either a 2- or 4-pyridyl group. The effect of protonisation of the pyridyl group would not make itself felt so strongly from the 3-pyridyl position as from the other positions, tautomeric transmission of charge not being possible in the first case. The evidence is not extensive, but it is clear that 4-3′-pyridylcinnoline is more readily formed than are the 2′- and the 4′-isomer. In the case of 1-*o*-aminophenyl-1-2′-pyridylethylene, it is evidently again necessary to balance the opposing factors of diazonium group stability and minimum protonisation of the pyridyl group to produce the optimum yield of cinnoline. A methyl group at the potential $C_{(3)}$-position assists the Widman–Stoermer cyclisation in these cases.



(V) (VI) (VII) (VIII)

As stated above, and described in the Experimental section, the diazotisation of 1-*o*-aminophenyl-1-phenyl-2-2′-quinolylethylene in hydrochloric acid is complicated. In dilute acid a small amount of the cinnoline was formed, together with a quantity of another compound which was isolated as its red picrate. Surprisingly, the yield of the cinnoline increased with acid concentration until in 8N-hydrochloric acid it could be isolated (as its picrate) in 52% yield. We can offer no explanation for the relatively large yield of the cinnoline in such circumstances, but the occurrence of a second reaction, with its possible effect upon the isolation of the cinnoline, makes it impossible to decide whether the yield of the latter really decreases with increasing acid concentration though this seems unlikely.

For the base corresponding to the red picrate the structures (IX; R = H), (IX; R = OH), and (X) require consideration. The first of these was eliminated by direct comparison of the red picrate with 1 : 1-diphenyl-2-2′-quinolylethylene picrate. 1-*o*-Methoxyphenyl-1-phenyl-2-2′-quinolylethylene was prepared from the corresponding alcohol, but an attempt to demethylate it with sodium (Prey, *Ber.*, 1943, **76**, 156) failed, and in any case analytical figures favour the expression (X). The latter can only be



(IX) (X) (XI)

accepted tentatively. The m. p. (94—95°) of the red picrate is surprisingly low, and the formation of (X) would imply cyclisation into a pyridine ring under conditions not particularly favourable to the Pschorr reaction. However, the work of Hey and Osbond (*J.*, 1949, 3164) shows that such cyclisation is not impossible, and the case is of sufficient theoretical interest to merit further examination.

Attempts to prepare cinnoline-4-aldehyde, a possible source of 4-4′-pyridylcinnoline, failed because of our inability to hydrolyse (XI), prepared from 4-methylcinnoline and *p*-nitrosodimethylaniline. Similarly, we were unable to isolate a homogeneous product on oxidising 4-methylcinnoline with selenium dioxide, or hydrolysing 4-(3 : 3 : 3-trichloro-2-hydroxypropyl)cinnoline (Alford and Schofield, *J.*, 1953, 1811).

Experiments on the chelating ability of some of the new cinnolines will be described by Dr. H. Irving. The bacteriostatic properties of a number of the compounds are tabulated below. The figures represent the concentrations in mg./100 c.c. which prevented visible

growth in Hedley Wright broth overnight at 37°. None of the compounds in the table had any action upon *P. berghei* or *T. equiperdum in vivo*. The first three compounds listed showed 1/20,000th, 1/10,000th, and 1/5,000th respectively of the spasmolytic action of atropine.

Cinnoline	Hæmolytic *Streptococcus*	*Staph. aureus*	*B. coli*	Approx. solubility (mg./100 c.c.)
4-*p*-Methoxyphenyl-3-2′-pyridyl- ...	0·3 [1]	>Sat. [2]	>Sat.	5
4-Phenyl-3-2′-pyridyl-	0·1 [1]	1·25 [1]	,,	5
4-*p*-Methoxyphenyl-3-2′-quinolyl- ...	1·25 [1]	>Sat.	>Sat.	2·5
6-Chloro-4-phenyl-3-2′-quinolyl-	5 [1]	,,	,,	5
4-3′-Pyridyl-	50	>50	>50	—
3-Methyl-4-3′-pyridyl-	>20	>20	>20	—

[1] The figures are approximate because of low solubility. [2] The sign > indicates lack of inhibition in saturated solution at pH 7·5, the figure representing the solubility.

We are indebted to Dr. F. Hawking of the National Institute of Medical Research, who arranged the bacteriostatic tests, and to Professor J. H. Burn, F.R.S., for the spasmolytic results. We are grateful to the Chemical Society, Imperial Chemical Industries Limited, and the Council of University College, Exeter, for financial support.

Washington Singer Laboratories,
Prince of Wales Road, Exeter.

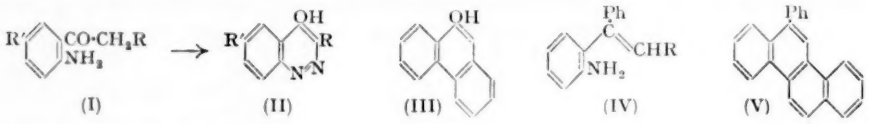
[*Received, June 1st,* 1953.]

NOTES.

745. *Cinnolines. Part XXXIII.* Some 3-Aryl-4-hydroxycinnolines.*

By D. W. Ockenden and K. Schofield.

The synthesis of 4-hydroxycinnolines (II) from 2-aminoaryl ketones (I) (cf. Schofield and Simpson, *J.*, 1945, 520) is widely applicable, and proceeds efficiently with the amines (I; R = H, halogen, or alkyl) (Schofield and Simpson, *loc. cit.*; *J.*, 1948, 1170; Keneford and Simpson, *J.*, 1948, 354). Hitherto, diazotisation of (I; R = aryl) has not been described; such reactions would be interesting because formally they present the possibility of competition between cinnoline formation and the Pschorr types of cyclisation (Pschorr, *Ber.*, 1896, **29**, 496). Thus, *o*-aminophenyl benzyl ketone (I; R = Ph, R′ = H) might



(I) (II) (III) (IV) (V)

provide either 4-hydroxy-3-phenylcinnoline (II; R = Ph, R′ = H) or 9-phenanthrol (III). The latter possibility was first suggested by Lothrop and Goodwin (*J. Amer. Chem. Soc.*, 1943, **65**, 363). We have recently synthesised some amines of the type (I; R = aryl) (Ockenden and Schofield, to be published) and now describe their behaviour on diazotisation.

Diazotisation of *o*-aminophenyl benzyl ketone in concentrated hydrochloric acid, and cyclisation of the diazonium compound, rapidly gave 4-hydroxy-3-phenylcinnoline in high yield. Under a variety of conditions appropriate to the Pschorr reaction (see Experimental) the cinnoline was the only product isolable. Similarly, the appropriate amines provided 4-hydroxy-6-methyl- (II; R = Ph, R′ = Me) and 4-hydroxy-6-nitro-3-phenyl-cinnoline (II; R = Ph, R′ = NO_2).

The behaviour of *o*-aminophenyl benzyl ketone in the present type of cinnoline synthesis recalls that of 1-*o*-aminophenyl-1 : 2-diphenylethylene (IV; R = Ph) which, upon diazotisation and cyclisation of the diazonium compound, gave only 3 : 4-diphenylcinnoline (Simpson,

* Part XXXII, *J.*, 1953, 3700.

J., 1943, 447). In contrast Simpson (*loc. cit.*) showed that diazotisation of 1-*o*-aminophenyl-2-α-naphthyl-1-phenylethylene (IV; R = 1-$C_{10}H_7$) gave either 3-α-naphthyl-4-phenylcinnoline or 2-phenylchrysene (V), depending on the conditions. For this reason we examined *o*-aminophenyl α-naphthylmethyl ketone (I; R = 1-$C_{10}H_7$, R′ = H). By diazotisation in concentrated hydrochloric acid and cyclisation of the diazonium compound this gave 4-hydroxy-3-α-naphthylcinnoline. Neither under any of the conditions mentioned for the phenyl analogue, nor by decompositions of the diazonium borofluoride (Heacock and Hey, *J.*, 1952, 1508) was 2-chrysenol produced.

Clearly, in amines of the type (I; R = aryl), the methylene group is highly activated, presumably so much so that cinnoline formation is rapid enough to exclude Pschorr cyclisation.

Experimental.—*3-Aryl-4-hydroxycinnolines.* The appropriate amine was diazotised at 0° with aqueous sodium nitrite, and the diazonium solution was then heated at 60° for 3 hr. The cinnoline quickly separated (Yield " A "). Alternatively the diazonium solution was kept at room temperature for 4 days (Yield " B ") (cf. Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 419).

Treatment of the diazonium chloride solution from *o*-aminophenyl benzyl ketone or *o*-aminophenyl α-naphthylmethyl ketone with copper powder (Pschorr, *loc. cit.*), or with sodium hypophosphite (Ruggli and Staub, *Helv. Chim. Acta*, 1937, **20**, 37), or diazotisation in alcoholic sulphuric acid with amyl nitrite and addition of copper powder (*idem, ibid.*) gave diminished yields of impure cinnolines.

No.	Cinnoline	Amine, g.	Conc. HCl, c.c.	$NaNO_2$, g.[a]	" A," %	" B," %
1	4-Hydroxy-3-phenyl-	0·2	5	0·07	64	90
2	4-Hydroxy-6-methyl-3-phenyl-	0·1	,,	0·04	67	86
3	4-Hydroxy-6-nitro-3-phenyl-...	0·25	10[b]	0·08	50	61
4	4-Hydroxy-3-α-naphthyl-	0·1	5	0·03	77	87

[a] In 1 c.c. of water, except in the third example (0·5 c.c.). [b] Acetic acid (6 c.c.) was also added. 1. White leaflets (Found: C, 76·7; N, 4·8; N, 12·1. Calc. for $C_{14}H_{14}ON_2$: C, 76·7; H, 4·5; N, 12·6%), m. p. 265—267° alone and mixed with a specimen prepared according to Schofield and Swain (*J.*, 1949, 2393). 2. Cream-coloured plates (Found: C, 77·7; H, 5·2. $C_{14}H_{12}ON_2$ requires C, 76·2; H, 5·1%), m. p. 310—312°. 3. The *compound* formed small yellow needles (Found: C, 64·1; H, 3·6. $C_{11}H_9O_3N_3$ requires C, 63·3; H, 3·4%), m. p. 347—348°. (4) The *compound* was obtained as small plates (Found: C, 78·2; H, 4·6. $C_{18}H_{12}ON_2$ requires C, 79·4; H, 4·4%), m. p. 285—286°.

We are indebted to the Council of University College, Exeter, and to Imperial Chemical Industries Limited for financial support, and to D.S.I.R. for a maintenance grant to one of us (D. W. O.).

WASHINGTON SINGER LABORATORIES,
PRINCE OF WALES RD., EXETER.

[*Received, June 1st*, 1953.]

746. *A New Synthesis of Arsonic Acids. Part IV.* Stilbene-3-arsonic Acid.*

By WALTER FREUND and ALFRED KOMZAK.

A SOLUTION of *m*-arsanilic acid (8·6 g.) in aqueous sodium hydrogen carbonate (60 c.c. containing 3·5 g.) was added to one of sodium nitrite (2·85 g.) in water (10 c.c.), and then diazotised with 25% hydrochloric acid (32·33 c.c.) in the usual manner. The filtered solution was added to cinnamic acid (5·9 g.) in acetone (120 c.c.), in which sodium acetate (approx. 32 g.) was suspended, the mixture was well shaken or stirred until the pH became approx. 6, and aqueous cupric chloride (8 g. in 18 c.c.) then added dropwise at room temperature. After 50 min. the precipitate was separated and purified by conventional methods. *Stilbene-3-arsonic acid* separated from acetic acid as pale yellow plates, which did not melt below 300° (Found: C, 55·55; H, 4·7, 4·7; As, 24·4, 24·3. $C_{14}H_{13}O_3As$ requires C, 55·3; H, 4·3; As, 24·6%).

THE UNIVERSITY, HOBART, TASMANIA.

[*Received, December 5th*, 1952.]

* Part III, *J.*, 1952, 3073.

747. *Studies with Phenylbutadiene. Part I. A New Synthesis of Naphthalene.*

By S. A. Faseeh.

A suspension of 4-phenylbutadiene-1-carboxylic acid (Doebner, *Ber.*, 1902, **35**, 2129) in carbon tetrachloride absorbs chlorine in sunlight (but not unless so irradiated), to yield successively 2 : 3-dichloro-5-phenylpent-4-enoic and 2 : 3 : 4 : 5-tetrachloro-5-phenylpentanoic acid (for a similar stepwise addition to 1-phenylbutadiene see Strauss, *Ber.*, 1909, **42**, 2866, and Muscat and Huggins, *J. Amer. Chem. Soc.*, 1929, **51**, 2496). Heating the former product with sodium carbonate solution yields 1-chloro-4-phenylbutadiene which affords naphthalene in 82% yield when heated with vacuum-dried stannous chloride.

This simple synthesis of naphthalene parallels that of phenanthrene from 2-formyldiphenyl (*Pakistan J. Sci. Res.*, 1951, **3**, 37; *J. Indian Chem. Soc.*, 1945, **22**, 181).

Experimental.—2 : 3-*Dichloro-5-phenylpent-4-enoic acid.* Chlorine was passed into 4-phenylbutadiene-1-carboxylic acid (43·5 g., 0·25 mole) in carbon tetrachloride (435 g.) in sunlight (37°). Absorption of 0·25 mole of chlorine required 1 hr., the suspension clearing and the temperature reaching 57°. A further 0·125 mole of chlorine was introduced during a further hour, and the solution was left for a third hour in sunlight. The yellow colour was lost and a small quantity of colourless crystals was deposited. The solution was filtered and evaporated in air to a viscous paste which was stirred with light petroleum–xylene. The resulting colourless precipitate, crystallised from the same mixture, yielded the *dichloro-acid* (57·7 g., 80%), m. p. 126—127° (Found : C, 53·5; H, 4·2; Cl, 29·3. $C_{11}H_{10}O_2Cl_2$ requires C, 53·9; H, 4·1; Cl, 29·0%).

2 : 3 : 4 : 5-*Tetrachloro-1-phenylpentanoic acid.* The foregoing conditions, modified by a final exposure to sunlight for 5 hr., gave the *tetrachloro-acid* (38·0 g., 95%), m. p. 180° (Found : C, 41·9; H, 3·3; Cl, 44·6. $C_{11}H_{10}O_2Cl_4$ requires C, 41·8; H, 3·2; Cl, 44·9%).

1-*Chloro-4-phenylbutadiene.* The dichloro-acid was heated in 5% sodium carbonate solution (225 c.c.) on the water-bath for 2 hr. An oil separated which was extracted with ether and on distillation yielded 1-chloro-4-phenylbutadiene (15·1 g., 92%), b. p. 113°/2—3 mm. (Found : C, 72·55; H, 5·1; Cl, 21·8. Calc. for $C_{10}H_9Cl$: C, 73·0; H, 5·5; Cl, 21·6%).

Naphthalene. 1-Chloro-4-phenylbutadiene (20·6 g.) and stannous chloride (2·35 g.; vacuum-dried) were gradually heated in an oil-bath. At 95° the mixture suddenly became brown and copious evolution of acid vapours took place. The temperature was kept at 95° for 2 hr., at the end of which evolution of acid vapours slackened. The temperature was then raised to *ca.* 220° and kept thereat for 0·5 hr. during which the evolution of gas came to an end. The product was heated with water and extracted with ether. The ethereal extract on distillation yielded naphthalene (13·1 g., 82%), m. p. and mixed m. p. 79° (from alcohol) [picrate, m. p. and mixed m. p. 149° (Found : C, 54·0; H, 3·2; N, 11·4. Calc. for $C_{16}H_{11}O_7N_3$: C, 53·8; H, 3·1; N, 11·8%)].

The author is indebted to Dr. Bashir Ahmad, Director of this Institute, for encouragement and facilities and to Mr. M. S. F. A. Abidi for assistance with the experiments.

University Institute of Chemistry,
University of the Panjab, Lahore, Pakistan. [*Received, May 18th*, 1953.]

748. *Attempted Preparation of Cyanogen Fluoride.*

By H. J. Callomon, H. W. Thompson, F. Allan Andersen, and Börge Bak.

The study of the infra-red and microwave spectra of cyanogen fluoride is of considerable interest, and attempts have been made to prepare it for this purpose in both Oxford and Copenhagen. Since the method described by Cosslett (*Z. anorg. Chem.*, 1931, **201**, 75) has been proved not to lead to this product, and other possible methods of preparation have also been unfruitful, a brief report seems desirable.

Cosslett's procedure, using the reaction $AgF + ICN = AgI + FCN$, was closely followed. Great care was taken to use only highly purified silver fluoride (Andersen, Bak, and Hillebert, *Acta Chem. Scand.*, 1953, **7**, 236) and cyanogen iodide (Bak and Hillebert, *Org. Synth.*, 1952, **32**, 29). The apparatus was so designed that volatile products were immediately trapped and not allowed to recycle over the silver fluoride with unchanged cyanogen iodide. This minimizes the chance of polymerization of any cyanogen fluoride formed. The products thus obtained were examined at Oxford in a Perkin-Elmer 12C infra-red spectrometer. Bands of carbon dioxide, nitrous oxide, silicon tetrafluoride, and carbonyl fluoride were identified in the complex spectrum. Essentially similar results were found at Copenhagen where a Beckman I.R.2 spectrometer was used, and where the gaseous products were also examined with a microwave spectroscope covering the range 18,000—26,000 Mc. Cyanogen fluoride should show the transition $J = 0 \longrightarrow J = 1$ at about 20,550 Mc if bond lengths r_{CF} and r_{CN} are 1·30 Å and 1·16 Å. No such absorption line could be found, although tests of the sensitivity with nitrous oxide proved quite satisfactory. The walls of the glass furnace were subsequently found to have been corroded in the vicinity of the silver fluoride. This could only have occurred after the introduction of cyanogen iodide gas into the furnace, for a preliminary baking out of the furnace with the silver fluoride *in situ* in high vacuum yielded only minute traces of gas.

At Oxford the experiments were then repeated, closely fitting liners of quartz and Monel-metal stainless steel tube being used, with the silver fluoride suspended on platinum gauze. The products were examined in a mass spectrometer. Those obtained from the experiment in quartz were identical with those obtained originally. Those obtained from the experiment in metal showed a decrease in the proportion of carbon dioxide, nitrous oxide, and silicon fluoride, but contained an appreciable proportion of carbon–fluorine and nitrogen–fluorine fragments. About 3% of a component with molecular weight 45 was found. Since no other combination of the possible atoms would correspond to this mass, after allowance for the ^{13}C and ^{15}N isotopes in carbon dioxide and nitrous oxide, the presence of a little cyanogen fluoride is indicated. A peak corresponding to the trimer $(FCN)_3$ was also obtained. Finally, the experiment was repeated with use of a liner of copper and mercuric fluoride, prepared from mercuric chloride and fluorine by Henne's method (*J. Amer. Chem. Soc.*, 1936, **58**, 884). The reaction proceeded at 100—150° and, in addition to products similar to those found previously, the mass-spectrum indicated the presence of components which appeared to arise from fluorination of the silicone tap-grease used on cone and socket joints on the external (cold) parts of the apparatus. A little cyanogen fluoride was again detected. A small amount of a blue gas, condensed by liquid air but not by solid carbon dioxide, was also formed which may have been CF_3NO (see Ruff, *loc. cit.*).

At Copenhagen a number of experiments were carried out in brass containers. Since preliminary experiments had shown that on use of such metal tubes the formation of $(FCN)_3$ was evident, implying a polymerization of the cyanogen fluoride first formed, attempts were made to freeze out the latter as quickly as possible. Silver fluoride and cyanogen iodide were mixed intimately and placed in the brass container which was immediately evacuated. The container was then placed in an oil-bath at 240° and the gases formed were withdrawn continuously through freezing traps. The product gave no indication of cyanogen fluoride in either the infra-red or the microwave spectrum.

During the attempts to mix silver fluoride and cyanogen iodide, it was noticed that they

form a complex compound very easily if mixed together in aqueous or anhydrous methanol. Yellow precipitates are formed, the composition corresponding to the formula $ICN,(AgF)_n$ where $1{\cdot}2 < n < 2{\cdot}8$, but no well-defined compound was ever obtained. These mixtures all exploded when heated to 220°, giving off mainly nitrogen, but no sign of cyanogen fluoride.

It would appear, therefore, that cyanogen fluoride cannot be prepared, except in very small yield, by direct fluorination of cyanides with strong fluorinating agents of the type here described. The point of attack appears to be the triple bond of the cyanide, for in the largest proportion of the products the carbon and nitrogen are separated. It appears unlikely that the active intermediate which attacks glass and quartz is cyanogen fluoride itself, for the presence of the latter was measured after some days of storage in a glass bulb. It would also be difficult to account for the formation of 10% of nitrous oxide with two nitrogen atoms adjacent, and very little nitrogen. Such cyanogen fluoride as is formed appears to polymerise very readily at higher temperatures to a stable trimer.

It is noteworthy that Ruff and Giese (*Ber.*, 1936, **69**, 598, 604, 684), by passing fluorine over silver or mercurous cyanides, obtained a mixture of carbon–nitrogen–fluorine compounds very similar to those reported here. Hückel (*Nachr. Akad. Wiss. Göttingen*, 1946, 36) attempted to fluorinate cyanogen iodide with mercuric fluoride under pressure in a steel bomb, and obtained the trimer $(FCN)_3$ in good yield. Attempts to prepare cyanogen fluoride by a reaction analogous to the Hofmann reaction starting with trifluoroacetyl chloride $CF_3{\cdot}COCl$, *viz.*, $CF_3{\cdot}COCl \longrightarrow CF_3{\cdot}CO{\cdot}NH_2 \longrightarrow CF_3{\cdot}N{:}CO \longrightarrow CF_3{\cdot}NH_2 \longrightarrow FCN$, stopped at $CF_3{\cdot}N{:}CO$, which is surprisingly stable.

THE PHYSICAL CHEMISTRY LABORATORY, OXFORD.
THE CHEMICAL LABORATORY, UNIVERSITY OF COPENHAGEN. [*Received, May 20th*, 1953.]

---

749. *The Synthesis of Monofluorocitric Acid.*

By D. E. A. RIVETT.

THE interest in monofluorocitric acid, suspected of being the metabolite responsible for the toxicity of fluoroacetate (for a recent review see Peters, *Proc. Roy. Soc.*, 1952, *B*, **139**, 143), has prompted its synthesis. Of the various methods used for the synthesis of citric acid that of Lawrence (*J.*, 1897, **71**, 457) appeared to be best suited for the preparation of a substituted citric acid even though a poor yield was to be expected. Thus, a Reformatsky reaction between ethyl ethoxalylfluoroacetate ($EtO{\cdot}CO{\cdot}CO{\cdot}CHF{\cdot}CO_2Et$) and ethyl bromoacetate produced ethyl monofluorocitrate, converted by acid hydrolysis into the extremely hygroscopic acid. Although the yield of ester is only about 12%, the starting materials are easily prepared.

Experimental.—Ethyl ethoxalylfluoroacetate. Ethyl fluoroacetate (122 g.) was added dropwise with stirring at room temperature during 1½ hr. to a mixture of ethyl oxalate (174 g.) and ether (400 ml.) containing alcohol-free sodium ethoxide (from 23 g. of sodium). 2 Days later 5N-hydrochloric acid (240 ml.), cooled to −20°, was rapidly added (slow addition results in greatly reduced yield of ester), the ether layer separated, and the residue twice extracted with ether. The combined ether extracts were washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. Distillation of the residue gave *ethyl ethoxalylfluoroacetate* as a pale yellow liquid (130 g., 55%), b. p. 99°/3 mm., n_D^{25} 1·4203 (Found: C, 47·2; H, 5·45. $C_8H_{11}O_5F$ requires C, 46·6; H, 5·4%). It gave a reddish-brown solution with ferric chloride, failed to form a copper derivative when shaken in chloroform solution with aqueous copper acetate, and, when kept with a buffered aqueous alcoholic solution of semicarbazide, gave a violet-coloured solution but no solid. The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in yellow needles, m. p. 145° (Found: C, 43·6; H, 4·0; N, 14·7. $C_{14}H_{15}O_8N_4F$ requires C, 43·5; H, 3·9; N, 14·5%).

Ethyl monofluorocitrate. A mixture of ethyl ethoxalylfluoroacetate (36·0 g.), ethyl bromo-

acetate (27·3 g.), and benzene (50 ml.) was added to activated zinc (13·6 g.) at such a rate as to maintain gentle reflux. After boiling under reflux for 1 hr. the solution was cooled and 3N-sulphuric acid (100 ml.) added, and the benzene layer was washed with aqueous sodium carbonate, dried, and evaporated. Distillation of the residue at 120°/10^{-1} mm. and redistillation *in vacuo* gave pure *ester* (6·0 g., 12%), n_D^{25} 1·4392 (Found: C, 49·4; H, 6·6. $C_{12}H_{19}O_7F$ requires C, 49·0; H, 6·5%), which crystallised after several weeks at 0°, forming needles, m. p. 41°. The yield of ester was not improved by increasing the proportion of zinc and of ethyl bromoacetate.

The ester (0·5 g.) was boiled under reflux with 3N-hydrochloric acid (15 ml.) for 6 hr. The acid was isolated by continuous extraction with ether and dried *in vacuo* for several days over phosphoric oxide. It forms very hygroscopic needles and because of difficulty in handling was converted into the barium salt. The acid was neutralised with 0·5N-sodium hydroxide, and hot aqueous barium chloride (0·8 g.; 5 ml.) was then added. The cooled solution was filtered and the residue washed with cold water till free from chloride ions, and the *barium fluorocitrate* (0·65 g.) dried at 110°/10 mm. [Found: Ba, 49·3. $(C_6H_4O_7F)_2Ba_3$ requires Ba, 49·9. $(C_6H_4O_7F)_2Ba_3,\frac{1}{2}H_2O$ requires Ba, 49·3%). For comparison barium citrate, prepared in the same way, was also analysed (Found: Ba, 51·5. Calc. for $(C_6H_5O_7)_2Ba_3$: Ba, 52·1. Calc. for $(C_6H_5O_7)_2Ba_3,\frac{1}{2}H_2O$: Ba, 51·6%).

The analyses were by Mr. F. E. Charlton. This paper is published by permission of the Chief Scientist, Ministry of Supply.

CHEMICAL DEFENCE EXPERIMENTAL ESTABLISHMENT,
PORTON, NR. SALISBURY.

[*Received, June 10th*, 1953.]

---

750. *A Method of Iodination.*

By K. T. POTTS.

IT has been customary in most types of iodination to employ in the reaction a third substance capable of acting as an hydrogen iodide acceptor. Ammonia has been used with success mainly by Datta and Prosad (*J. Amer. Chem. Soc.*, 1917, **39**, 441) and Bordeianu (*Ann. Sci. Univ. Jassy*, 1935, **20**, 131; *Chem. Abs.*, 1936, **30**, 1760) who found that phenol could be iodinated in the presence of ammonia, methylamine, or tetramethylammonium hydroxide. Clayton, Hems, and Borroughs (*J.*, 1949, 3424; 1950, 840) have substituted a primary amine for ammonia and have successfully developed a method of using iodine–potassium iodide solution in the presence of ethylamine; they found that the primary amine was more suitable than the corresponding secondary and tertiary amines.

Reactant	Product *	Yield, %	M. p.
Aniline	*p*-Iodoaniline	76	61—62°
p-Toluidine	3-Iodo-*p*-toluidine	35	40
Dimethylaniline	*p*-Iododimethylaniline	86	78—79
Phenol	2 : 4 : 6-Tri-iodophenol	72	155—156
o-Cresol	4 : 6-Di-iodo-*o*-cresol	quant.	67
m-Cresol	2 : 4 : 6-Tri-iodo-*m*-cresol	73	121
p-Cresol	2 : 6-Di-iodo-*p*-cresol	quant.	60
β-Naphthol	1-Iodo-2-naphthol	96	92
o-Nitrophenol	2 : 4-Di-iodo-6-nitrophenol	66	96
p-Nitrophenol	2 : 6-Di-iodo-4-nitrophenol	34	153—155
p-Hydroxybenzoic acid	3 : 5-Di-iodo-4-hydroxybenzoic acid	53	264—265 †
Salicylic acid	3 : 5-Di-iodosalicylic acid	—	decomp. 220—240
Anthranilic acid	2-Amino-5-iodobenzoic acid	76	212
Pyrrole	Tetraiodopyrrole	41	decomp. 150—160

Products had m.p.s agreeing with the literature values, except for that from salicylic acid [lit.: values range from 212° (decomp.) to 235—236°] and from pyrrole (lit.: 145°).

* Cresols are numbered OH = 1. † Loses iodine above 200°.

In an investigation of the iodination of a derivative of tyrosine, use was made of iodine–potassium iodide solution in the presence of ethylenediamine. This reagent was found to

be very satisfactory for the iodination of phenols, amines, and hydroxybenzoic and other acids. The scope of the method is largely limited by the ease with which the compounds to be iodinated undergo substitution which depends on the presence of electron-repelling groups in the nucleus. Highly reactive compounds, such as phenol, always gave the tri-substituted compound even when one equivalent of the reagent was used. Ethers, such as anisole and methyl β-naphthyl ether, failed to react (cf. Jones and Richardson, *J.*, 1953, 713); acetanilide, *p*-nitroaniline, and thiophen did not react appreciably. The method is of particular value for preparing *p*-iodoaniline. The table summarizes the main results obtained.

Experimental.—It was found convenient to use a stock 4N-solution of iodine in potassium iodide and a 60% aqueous solution of ethylenediamine. In most experiments a solution of iodine in potassium iodide (0·1 mole) was added, with constant shaking, to a solution of the aromatic compound (0·1 mole) in ethylenediamine solution (0·05 mole). Alcohol (*ca.* 10 ml.) was added if necessary to form a homogeneous phase. The solution was allowed to decolorize before the next addition of iodine was made. After 2 hr. at room temperature the mixture was poured into water containing sodium thiosulphate. If a crystalline product separated, it was filtered off and recrystallized from a suitable solvent, usually alcohol or acetic acid. If the product separated as an oil, a slight excess of alkali was added, and the product steam-distilled.

THE UNIVERSITY OF SYDNEY, SYDNEY, AUSTRALIA. [*Received, June 16th*, 1953.]

---

751. *Infra-red Absorptions of the* iso*Cyanate Group.*

By W. H. T. DAVISON.

THE infra-red absorptions of the *iso*cyanate group have not been previously characterised, apart from a general (and erroneous) assignment of the region 2050—2200 cm.$^{-1}$ to "*iso*-cyanates, 1 : 2-dienoid, etc." (Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397), and assignments for cyanic acid (Herzberg and Reid, *Discuss. Faraday Soc.*, 1950, **9**, 92) and methyl *iso*cyanate (Eyster and Gillette, *J. Chem. Phys.*, 1940, **8**, 369). The last two papers discuss in some detail the interaction of the pseudo-symmetrical vibrations $\nu_{C=O}$ and $\nu_{C=N}$ to give one very strong anti-symmetrical absorption $\nu_{a(NCO)}$ at about 2250 cm.$^{-1}$ and a weaker symmetrical absorption $\nu_{s(NCO)}$ at about 1350 cm.$^{-1}$ (the convenient notation is that of Thomas, *Chem. and Ind.*, 1953, 567). The spectra of eight *iso*cyanates have been

	cm.$^{-1}$	prism	ε *
1. Cyanic acid [a]	2289, 2260	LiF	(vs)
2. Methyl *iso*cyanate [b]	2230 [c]	KBr	(s)
3. Phenyl *iso*cyanate	2274, 2263	LiF	(vs)
	2270	NaCl	(vs)
4. 1-Naphthyl *iso*cyanate ...	2275	LiF	2000
	2270	NaCl	1200
5. 2-Naphthyl *iso*cyanate	2267	LiF	(vs)
6. Octadecyl *iso*cyanate	2270	NaCl	(vs)
7. Naphthalene 1 : 5-di*iso*-cyanate	2265	LiF	1900
	2270	NaCl	1400
8. Toluene di*iso*cyanate	2265	LiF	(vs)
9. Methylenebis-(*p*-phenyl *iso*cyanate)	2272	LiF	(vs)
10. Hexamethylene di*iso*-cyanate	2270	LiF	(vs)

[a] Herzberg and Reid, *loc. cit.*; measured as a gas. [b] Eyster and Gillette, *loc. cit.*; measured as a gas. [c] Of doubtful accuracy since the prism has poor dispersion in this region.

* $\varepsilon = \log_{10}(I_0/I)/nbc$ where n is the number of NCO groups per molecule, b is the path length in cm., and c is the concentration in moles/l. Where not measured quantitatively, (vs) denotes very strong and (s) strong absorption.

examined for these stretching vibrations; the absorptions associated with the bending modes, which would probably be in the potassium bromide region, were not investigated.

Spectra of solutions in carbon tetrachloride were measured with a double-beam Grubb-

Parsons spectrometer, sodium chloride and lithium fluoride prisms being used; the results for $\nu_{a(NCO)}$ are given in the Table, together with those for cyanic acid and methyl *iso*cyanate, from the literature. Frequency calibration was based upon the rotational fine structure of carbon monoxide and carbon dioxide.

The results show that $\nu_{a(NCO)}$ gives an extremely intense characteristic absorption at 2269 ± 6 cm.$^{-1}$. In all cases, the frequency was re-measured with a capillary thickness of the undiluted liquid, or a paraffin mull of the solid *iso*cyanate; although it was difficult to obtain samples thin enough for accurate measurements, the frequencies were the same as those of the carbon tetrachloride solutions. Values of the group molar absorptivity (ε) were about 1300 with the normal slits required for sodium chloride working and about 2000 for lithium fluoride working. While it might have been expected that ε would be of the order of twice that for a typical $\nu_{C=O}$, or $\nu_{C\equiv N}$, the measured values are much stronger, and so permit extremely sensitive analyses (the more so as the 2270-cm.$^{-1}$ region is spectrally transparent for most compounds). Nitriles absorb in the same region (Kitson and Griffith, *Analyt. Chem.*, 1952, **24**, 334), but they have in general lower frequencies (2250 ± 10 cm.$^{-1}$ for unconjugated nitriles) and very much weaker absorptions ($\varepsilon \sim 13$). Unlike $\nu_{C\equiv N}$, $\nu_{a(NCO)}$ is apparently unaffected by adjacent unsaturation.

It would obviously be of value to be able to distinguish *iso*cyanates from nitriles by means of other characteristic bands of the former, and so the 1300—1400 cm.$^{-1}$ region was examined for $\nu_{s(NCO)}$. Tentative assignments of weak absorptions occurring at 1380—1395 (in compounds 3—5 and 7) were made, but the bands were too weak to be of general diagnostic value, especially as they were liable to be hidden by the 1375-cm.$^{-1}$ bands associated with methyl and methylene deformations. This assignment corresponds to that of $\nu_{s(NCO)}$ at 1377 cm.$^{-1}$ in methyl *iso*cyanate (Eyster and Gillette, *loc. cit.*).

The author thanks Mr. G. R. Bates for experimental assistance, and the Dunlop Rubber Co. Ltd. for permission to publish this note.

CHEMICAL RESEARCH DIVISION, DUNLOP RESEARCH CENTRE,
BIRMINGHAM, 24. [*Received, June 19th*, 1953.]

---

752. *The Interaction of Iodine Bromide and Phenol or Aniline.*

By A. G. SHARPE.

IODINE BROMIDE and phenol react in carbon tetrachloride according to equation (1) (Militzer, *J. Amer. Chem. Soc.*, 1938, **60**, 256):

$$C_6H_5{\cdot}OH + 2IBr \longrightarrow p\text{-}C_6H_4Br{\cdot}OH + HBr + I_2 \quad . \quad . \quad (1)$$

The formulation of the overall reaction as the sum of (2) and (3) appeared to be supported by the formation (in unspecified yield) of *p*-bromoaniline hydriodide in the interaction of

$$C_6H_5{\cdot}OH + Br \longrightarrow p\text{-}C_6H_4Br{\cdot}OH + HI \quad . \quad . \quad . \quad (2)$$
$$HI + IBr \longrightarrow HBr + I_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

iodine bromide and aniline. Reaction (2), however, would imply polarization of the iodine–bromine bond in the unlikely direction I^-Br^+; and it has been suggested [Lambourne and Robertson, *J.*, 1947, 1167; Bennett and Sharpe, *J.*, 1950, 1383 (where physicochemical data are given)] that reaction (1) is one of bromination by the bromine formed in the thermal dissociation of iodine bromide, which takes place to the extent of 9·5% in carbon tetrachloride at 25°. A third suggestion, that the mechanism of (1) is represented by (4) and (5), has recently been made by Pearson and Ross (*J. Amer. Chem. Soc.*, 1952, **74**, 2933).

$$C_6H_5{\cdot}OH + IBr \longrightarrow p\text{-}C_6H_4I{\cdot}OH + HBr \quad . \quad . \quad . \quad . \quad (4)$$
$$2p\text{-}C_6H_4I{\cdot}OH + HBr \longrightarrow p\text{-}C_6H_4Br{\cdot}OH + C_6H_5{\cdot}OH + I_2 \quad . \quad (5)$$

These authors have shown that, in carbon tetrachloride, reaction (5) is complete after 85 min. at 45° or 8—10 hr. at room temperature—conditions similar to those described by Militzer for the bromination of α-naphthol with iodine bromide in carbon tetrachloride.

It is now shown by quantitative analysis that phenol and iodine bromide in carbon tetrachloride react rapidly at room temperature. There is immediate evolution of hydrogen bromide, and the colour of iodine at once appears in the solution; after 10 min., half of the oxidising power of the iodine bromide has disappeared, and half of the bromine (but no iodine) has entered the aromatic nucleus. No further change occurs during 24 hr. Even after 30 sec., the reaction is about 80% complete. These periods are so much shorter than that required for (5) that Pearson and Ross's mechanism appears untenable.

After iodine bromide and excess of aniline have been allowed to react during 2 min. at room temperature, the solution possesses no oxidising properties, and a mole of iodine bromide yields 0·5 g.-ion each of Br^- and I^-. Aniline forms a complex with iodine in carbon tetrachloride solution, and then reacts with it even at room temperature (Hofmann, *Annalen*, 1848, **67**, 61; Hodgson and Marsden, *J.*, 1937, 1365); when solutions of aniline (0·02 mol.) and iodine bromide (0·04 mol.) are mixed, however, a strong but transient iodine colour appears. It seems possible, therefore, that thermal dissociation of the iodine bromide is followed by a very fast reaction between bromine and aniline and a somewhat slower reaction between iodine and aniline. The overall change is expressed by the equation,

$$2C_6H_5{\cdot}NH_2 + 2IBr \longrightarrow C_6H_4Br{\cdot}NH_2 + C_6H_4I{\cdot}NH_2 + HBr + HI \quad . \quad (6)$$

The stoicheiometry of (6) is therefore fundamentally different from that of (1); and Militzer's isolation of *p*-bromoaniline hydriodide may thus be explained without postulating that the iodine bromide reacts as I^-Br^+. Although the experiments described here do not eliminate the possibility of iodine bromide reacting as I^-Br^+, they do appear to show that the established thermal dissociation of iodine bromide affords a satisfactory alternative explanation for the course of its reactions with aromatic compounds.

Experimental Methods.—A solution of iodine bromide in carbon tetrachloride was standardised by shaking it with aqueous potassium iodide and titrating the liberated iodine with 0·2N-thiosulphate. Aliquot portions were allowed to react with phenol or aniline in carbon tetrachloride, and residual oxidising power was determined as before. Control experiments showed that when the iodine bromide solution was shaken with an aqueous solution containing both phenol and potassium iodide, iodine liberation was 95% of the theoretical; the possibility that any significant part of the reaction with phenol took place after addition of the potassium iodide solution was thereby eliminated.

For the determination of halides after reactions, the carbon tetrachloride solution was shaken with sulphurous acid. Total halide in the aqueous extract was determined by Volhard's method, and iodine by selective oxidation with excess of hydrogen peroxide and acetic acid (Mitchell, "Sutton's Volumetric Analysis," J. and A. Churchill, London, 1935, p. 256). In a typical experiment with phenol, in which solutions of 5 g. (excess) of phenol and 0·0240 mole of iodine bromide in 100 ml. carbon tetrachloride at 20° were allowed to react during 10 min., the products (*a*) liberated 0·0122 mole of iodine from potassium iodide and (*b*) after reduction with sulphurous acid contained 0·0355 g.-ion of total halide, of which 0·0230 g.-ion were iodide. With a reaction period of 30 sec., the products liberated 0·0146 mole of iodine. Other results are presented in outline above.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, June 19th*, 1953.]

753. *Bond Type in Trisacetylacetonecobalt*(III).

By Richard O. Whipple, Robert West, and Kenneth Emerson.

B. West (*J.*, 1952, 3122) has recently indicated the need for a redetermination of the magnetic susceptibility of trisacetylacetonecobalt(III) in order to make clear the nature of the bonding in this compound. The only previously reported measurement, by Ishiwara (*Rep. Tohoku Univ.*, 1914, **3**, 309), indicates paramagnetism amounting to 0·93 Bohr magneton. This is not consistent with either d^2sp^3 hybrid bonds (which should lead to diamagnetism) or with the "ionic" structure (which should have four unpaired electrons).*

The present authors have determined the magnetic susceptibility of trisacetylacetonecobalt(III) and find it to be diamagnetic. Therefore, the compound is very probably an octahedral penetration complex of the usual type with d^2sp^3 hybrid covalent bonding. The slow cobalt exchange noted by West (*loc. cit.*) for this compound is not surprising in view of the large electronegativity difference between cobalt and oxygen, and the resulting ionic character of the Co–O bonds.

An interesting parallel to this case of conflicting magnetic data is afforded by the related compound, tripotassium cobalt(III) oxalate. The original report of diamagnetism for this compound (Wiedemann, *Ann. Physik*, 1887, **32**, 459) was first contradicted (Berkman and Socher, *Z. phys. Chem.*, 1926, **124**, 324) and later confirmed (Johnson, *Trans. Faraday Soc.*, 1932, **28**, 848). The results of Berkman and Socher and those of Ishiwara (*locc. cit.*) can probably be ascribed to paramagnetic or ferromagnetic impurities, which are often persistent contaminants in compounds of the transition metals.

Experimental.—Trisacetylacetonecobalt(III). Chloropentamminocobalt(III) dichloride (10 g.) was dissolved in hot water (400 ml.), and the pH adjusted to approx. 8 by addition of 2N-sodium hydroxide. Acetylacetone (50 g.) was added, and the solution was heated on the steam-bath until long, green needles of product appeared (about 30 min.). The mixture was then cooled and extracted several times with benzene. The combined extracts were dried and evaporated to give black crystals. The product (from several similar preparations) was recrystallized three times from absolute ethanol and twice from benzene; the final recrystallization was carried out shortly before the magnetic measurements were made. The compound melted at 198·5° (corr.) (Found: Co, 16·3; C, 50·7; H, 6·1. Calc. for $C_{15}H_{21}O_6Co$: Co, 16·5; C, 50·6; H, 5·9%). West (*loc. cit.*) found m. p. 196° (uncorr.) and Urbain and Debierne (*Compt. rend.*, 1899, **129**, 302) give 240°.

Magnetic measurements. These were made by the Gouy split-tube method, water and air being used as standards. Three packings of the tube were made, and measurements were carried out at six field strengths between 7000 and 12,000 gauss. The susceptibilities obtained were independent of field strength. The volume susceptibility at 27·4° was $-0{\cdot}159 \times 10^{-6}$ c.g.s. unit, corrected for air in the sample. This corresponds to a gram-susceptibility of $-0{\cdot}167 \times 10^{-6}$ and a molar susceptibility of $-59{\cdot}4 \times 10^{-6}$ c.g.s. unit.

Mallinckrodt Laboratory, Harvard University,
Cambridge 38, Massachusetts, U.S.A.

[*Received, June 29th*, 1953.]

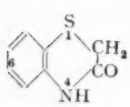
* West suggests a third possible structure involving d^3 hybrid bonds. Such a structure would, however, be diamagnetic, and not paramagnetic as he suggests.

754. *Preparation of 2 : 3-Dihydro-3-oxobenzo-1 : 4-thiazine Derivatives as Possible Anthelmintics. Part II.**

By Alexander Mackie and A. Anthony Cutler.

Since many derivatives of 2 : 3-dihydro-3-oxobenzo-1 : 4-thiazine (I) show distinct anthelmintic effects when tested *in vitro* against liver fluke (*Fasciola hepatica*) (Mackie and Raeburn, *Brit. J. Pharmacol.*, 1952, **7**, 219), the earlier work in this series (*idem*, *J.*, 1952, 787; Mackie and Cutler, *Rec. Trav. chim.*, 1952, **71**, 1198) has been extended, particularly to 6-substituted compounds.

The 6-bromo-, 6-methyl, and 6-*tert.*-butyl derivatives were obtained by reduction of the corresponding *para*-substituted (*o*-nitrophenylthio)acetic acids. These acids were prepared by treating the appropriate diazotised *o*-nitro-amine with mercaptoacetic acid in presence of aqueous sodium acetate and decomposing the (phenyldiazothio)acetic acids thus obtained by hot aqueous sodium carbonate (cf. Friedlaender and Chwala, *Monatsh.*, 1907, **28**, 279). Previous attempts to prepare the 6-bromo-compound either by Sandmeyer reaction or by decomposition of the diazonium perbromide resulted only in highly impure material.



(I)

6-Toluene-*p*-sulphonamido-, 6-acetamidobenzenesulphonamido-, and 6 : 7-diethoxy-derivatives of (I) were also prepared.

Analogy with known anthelmintics led to unsuccessful attempts to condense the 6-chloro-derivative of (I) with 2-diethylaminoethylamine, and the 6-amino-derivative with 10-chloroacetylphenothiazine, and to prepare the 6 : 7-dichloro-derivative of (I) from the 6 : 7-dihydroxy-compound.

The derivatives prepared showed only depressant or no effect when tested against anterior preparations of the roundworm *Ascaris lumbricoides*, but some had a paralysant effect on liver fluke (*Fasciola hepatica*) *in vitro*, the 6-bromo-derivative being very effective (1 : 20,000). Details of these tests will be published elsewhere.

Experimental.—**6-*Chloroacetoamido*-2 : 3-*dihydro*-3-*oxobenzo*-1 : 4-*thiazine*.** Chloroacetyl chloride (6 g.) was slowly added to a boiling glacial acetic acid solution (150 c.c.) of 6-amino-2 : 3-dihydro-3-ketobenzo-1 : 4-thiazine (7 g.), and the mixture refluxed for 30 min. Pouring the cooled product into cold water gave the pale brown *chloroacetoamido*-derivative, which crystallised from aqueous ethanol as colourless needles (4 g.), m. p. 240—241° (decomp.) (Found : N, 11·1. $C_{10}H_9O_2N_2ClS$ requires N, 10·9%).

6-*Benzamido*-2 : 3-*dihydro*-3-*oxobenzo*-1 : 4-*thiazine*. Benzoyl chloride (15 c.c.) was added portionwise to vigorously agitated 6-amino-2 : 3-dihydro-3-oxobenzo-1 : 4-thiazine (5 g.) suspended in aqueous sodium hydroxide (175 c.c.). The precipitated *benzamido*-derivative crystallised from acetic acid in colourless needles (3 g.), m. p. 269—270° (decomp.) (Found : N, 9·6. $C_{15}H_{12}O_2N_2S$ requires N, 9·9%).

2 : 3-*Dihydro*-3-*oxo*-6-*toluene*-p-*sulphonamidobenzo*-1 : 4-*thiazine*. A pyridine solution (30 c.c.) of the 6-amino-compound (4·5 g.) was refluxed with toluene-*p*-sulphonyl chloride (7 g.) for 2 hr. The dark brown precipitate was dissolved in 0·1N-sodium hydroxide (200 c.c.), diluted to 600 c.c., refluxed with charcoal, and filtered. The filtrate was added slowly to excess of dilute sulphuric acid and recrystallization of the resulting precipitate from aqueous ethanol gave colourless needles (3 g.) of the pure *toluenesulphonamido-thiazine*, m. p. 235—236° (decomp.) (Found : N, 8·3. $C_{15}H_{14}O_3N_2S_2$ requires N, 8·4%).

6-p-*Acetamidobenzenesulphonamido*-2 : 3-*dihydro*-3-*oxobenzo*-1 : 4-*thiazine*. *p*-Acetamidobenzenesulphonyl chloride (6 g.) was refluxed for 1 hr. with a pyridine solution (15 c.c.) of the 6-amino-derivative (4·5 g.). The product was refluxed with acetone (200—250 c.c.), then filtered hot, and, on addition of water, the required *compound* was precipitated. It formed pale yellow feathery needles (5 g.), m. p. 305° (decomp.), from nitrobenzene (Found : N, 10·9. $C_{16}H_{15}O_4N_3S_2$ requires N, 11·1%).

6 : 7-*Diethoxy*-2 : 3-*dihydro*-3-*oxobenzo*-1 : 4-*thiazine*. A solution of 2 : 3-dihydro-6 : 7-di-

* *J.*, 1952, 787, is considered to be Part I of this series.

hydroxy-3-oxobenzo-1 : 4-thiazine (5 g.) (Mackie and Raeburn, *J.*, 1952, 787) in ethanolic sodium ethoxide (50 c.c.) was refluxed (2—3 hr.) with ethyl sulphate (12 g.) in an inert atmosphere. After cooling and dilution with water, the product was filtered off, dissolved in hot benzene (charcoal), and filtered. Light petroleum (b. p. 60—80°) precipitated the **6 : 7-*diethoxythiazine*** which formed pale yellow rectangular prisms (0·3 g.), m. p. 136—137°, from aqueous ethanol (Found : C, 56·4; H, 6·1. $C_{13}H_{15}O_3NS$ requires C, 56·2; H, 6·3%).

6-*Bromo*-2 : 3-*dihydro*-3-*oxobenzo*-1 : 4-*thiazine.* 4-Bromo-2-nitroaniline (40 g.) was diazotised and the solution added to a well-cooled mixture of mercaptoacetic acid (25 g.) and aqueous sodium acetate (containing 60 g.). A solution in aqueous sodium carbonate of the thick red oil obtained was decomposed on warming, and acidification of the aqueous solution of the product afforded a bright yellow precipitate of the crude (4-*bromo*-2-*nitrophenylthio*)*acetic acid* (19 g.), which was sufficiently pure for the reduction. It crystallised from aqueous ethanol as yellow needles, m. p. 216—217° (Found : C, 33·3; H, 2·0; N, 4·9. $C_8H_6O_4NBrS$ requires C, 32·9; H, 2·1; N, 4·8%).

Reduction of this acid gave the 6-bromo-thiazine, colourless needles (8 g.), m. p. 204—205° (from aqueous ethanol) (Found: C, 39·3; H, 2·5; N, 5·5. Calc. for C_8H_6ONBrS: C, 39·3; H, 2·5; N, 5·7%). Mackie and Raeburn (*loc. cit.*) gave the m. p. of the supposedly impure bromo-compound as 220°, with a nitrogen content of 5·0%, but there appears to be no doubt that the compound obtained by the above method is pure bromo-derivative.

(4-*Methyl*-2-*nitrophenylthio*)*acetic acid*, similarly prepared from 3-nitro-4-aminotoluene (20 g.), crystallised from aqueous ethanol as yellow needles (6 g.), m. p. 182—183° (Found : C, 47·7; H, 4·0; N, 6·2. $C_9H_9O_4NS$ requires C, 47·6; H, 4·0; N, 6·2%), and on reduction afforded the **6-*methyl-thiazine***, pale cream-coloured needles (4 g.) (from aqueous acetic acid), m. p. 178—179° (partial decomp.) (Found : C, 60·6; H, 5·1; N, 8·0. C_9H_9ONS requires C, 60·3; H, 5·0; N, 7·8%).

6-tert.-*Butyl*-2 : 3-*dihydro*-3-*oxobenzo*-1 : 4-*thiazine.*—4-*tert.*-Butyl-2-nitroaniline (10 g.) (Shoesmith and Mackie, *J.*, 1928, 2336) gave (4-tert.-*butyl*-2-*nitrophenylthio*)*acetic acid*, yellow needles (1 g.), m. p. 162—163° (from aqueous ethanol) (Found : C, 53·4; H, 5·6. $C_{12}H_{15}O_4NS$ requires C, 53·5; H, 5·6%), and thence the **6-tert.-*butyl-thiazine***, colourless plates (0·2 g.), m. p. 170—171° (from aqueous ethanol) (Found : C, 63·7; H, 6·8; N, 6·0. $C_{12}H_{15}ONS$ requires C, 65·2; H, 6·8; N, 6·3%).

The authors thank the Agricultural Research Council for a grant, Professor F. Bell for his interest, Dr. J. W. Minnis for some of the microchemical analyses, and Dr. J. Raeburn for the preparation of one of the compounds.

HERIOT-WATT COLLEGE, EDINBURGH. [*Received, July 7th*, 1953.]

---

755. *Phenylthiohydantoins from Serine and Threonine.*

By V. M. INGRAM.

DURING the stepwise degradation of peptides by Edman's method (*Acta Chem. Scand.*, 1950, **4**, 283) the amino-acids appear as the corresponding substituted 3-phenyl-2-thiohydantoins. Authentic samples of most of these derivatives are readily prepared (*idem, ibid.*, p. 277), but threonine has so far only yielded the dehydrated analogue, 5-ethylidene-3-phenyl-2-thiohydantoin, and attempts to isolate the serine derivative were unsuccessful (*idem, locc. cit.*; Swan, *Australian J. Sci. Res.*, *A*, 1952, **5**, 719). By using milder conditions the pure phenylthiohydantoins from these two amino-acids have now been isolated, and the products of hydrolysis have been briefly examined.

Experimental.—From serine. DL-Serine (1·0 g.) was treated with phenyl *iso*thiocyanate, Edman's method (*ibid.*, p. 277) being used at room temperature. Excess of reagent was removed by several extractions with benzene, and acid was added until the pH was 1; some pink oil separated and was discarded. *5-Hydroxymethyl-3-phenyl-2-thiohydantoin* was deposited during 2 days at room temperature and was recrystallised from ethanol; the derivative

(0·9 g.) then had m. p. 176—178° (Found: C, 53·9; H, 4·5; N, 12·5. $C_{10}H_{10}O_2N_2S$ requires C, 54·1; H, 4·5; N, 12·6).

From threonine. By the same procedure DL-threonine (0·5 g.) was converted into *5-1′-hydroxyethyl-3-phenyl-2-thiohydantoin*, which formed felted needles (0·55 g.) (from ethanol), m. p. 194° (decomp.; after charring at 150°) (Found: C, 55·5; H, 4·9; N, 11·8. $C_{11}H_{12}O_2N_2S$ requires C, 55·9; H, 5·1; N, 11·9).

Both phenylthiohydantoins were examined by paper chromatography in two of the solvent systems recommended by Sjöquist (*Acta Chem. Scand.*, 1953, **7**, 447). The following relative R_F values (3-phenyl-2-thiohydantoin, $R_F = 1·00$) were found for the serine and the threonine derivatives: in heptane–pyridine, 0·77 and 1·00, respectively; in heptane–*n*-butanol–formic acid (2 : 2 : 1), 0·82 and 0·97, respectively.

Hydrolysis. Hydrolysis at 150° of the phenylthiohydantoin (10 micromoles) from serine in hydrobromic acid (47%; 1 c.c.; 24 hr.) or aqueous barium hydroxide (0·25 N; 2 c.c.; 48 hr.) yielded a mixture of alanine and serine in variable proportions. Under similar conditions the threonine compound formed mainly α-aminobutyric acid and some glycine in hydrobromic acid; when heated with aqueous barium hydroxide, threonine appeared together with smaller quantities of glycine and α-aminobutyric acid. The amino-acids were identified by paper chromatography, *n*-butanol–acetic acid–water (3 : 1 : 1) and Hausmann's *sec*-butanol–ammonia and *sec*.-butanol–formic acid (*J. Amer. Chem. Soc.*, 1952, **74**, 3181) being used.

MEDICAL RESEARCH COUNCIL UNIT FOR THE STUDY OF THE MOLECULAR STRUCTURE OF BIOLOGICAL SYSTEMS, CAVENDISH LABORATORY, CAMBRIDGE.

[*Received, July 9th*, 1953.]

---

756. *Azulenes. Part I. A Synthesis of Azulene.*

By DOUGLAS LLOYD and FREDERICK ROWE.

bicyclo[5 : 3 : 0]DEC-7-EN-9-ONE, prepared by the method described by Islam and Raphael (*J.*, 1952, 4086) for *bicyclo*[4 : 3 : 0]non-6-en-8-one, has been converted into the corresponding *bicyclo*[5 : 3 : 0]decenol and *bicyclo*[5 : 3 : 0]decadiene. The latter, when dehydrogenated over palladium–charcoal in a vacuum (see Gordon, *Chem. Reviews*, 1952, **50**, 168), yielded a main product which was identified as azulene by means of its ultraviolet spectrum.

Experimental.—Ethyl 1-acetonyl-2-oxocycloheptane-1-carboxylate. This was prepared essentially by Islam and Raphael's method (*loc. cit.*). Propargyl bromide was condensed with the sodium derivative of ethyl 2-oxo*cyclo*heptane-1-carboxylate to give ethyl 2-oxo-1-propargyl-*cyclo*heptane-1-carboxylate, which was then converted into ethyl 1-acetonyl-2-oxo*cyclo*heptane-1-carboxylate, b. p. 134°/2 mm. The *bis-2 : 4-dinitrophenylhydrazone* formed yellow prisms, m. p. 175°, from methanol–ethyl acetate (Found: C, 50·1; H, 4·9; N, 18·7. $C_{25}H_{28}O_{10}N_8$ requires C, 50·0; H, 4·7; N, 18·7%). The *disemicarbazone* could not be satisfactorily recrystallised, but a dust-free sample, purified by washing it, had m. p. 223° (decomp.) (Found: C, 51·3; H, 7·7; N, 23·2. $C_{15}H_{26}O_4N_6$ requires C, 50·8; H, 7·35; N, 23·7%).

bicyclo[5 : 3 : 0]*Dec-7-en-9-one.* Ethyl 1-Acetonyl-2-oxo*cyclo*heptane-1-carboxylate (4·2 g.) was heated under reflux with aqueous potassium hydroxide solution for 6 hr. in nitrogen (cf. Islam and Raphael, *loc. cit.*). The product (2·0 g., 76%), b. p. 94°/2 mm., formed a *dinitrophenylhydrazone* as red needles [from light petroleum (b. p. 80—100°)], m. p. 185° (Found: C, 58·6; H, 5·5; N, 16·8. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·45; N, 17·0%).

bicyclo[5 : 3 : 0]*Dec-7-en-9-ol.* The *bicyclo*[5 : 3 : 0]decenone (2·0 g.) was reduced with lithium aluminium hydride, giving a faintly yellow oil, b. p. 88—92°/2 mm. (1·55 g., 76·5%). Various attempts to dehydrogenate this oil, by using sulphur, selenium, chloranil, and palladium–charcoal, were ineffective; heating of a sample under reflux with nitrobenzene and iodine (cf. Treibs, *Annalen*, 1952, **576**, 110) produced an intense green material, which was soluble in phosphoric acid, and could be separated readily by paper chromatography, but faded rapidly in air.

bicyclo[5 : 3 : 0]*Deca*-7 : 9-*diene*. *bicyclo*Decanol (1·2 g.) was heated with freshly fused, powdered potassium hydrogen sulphate (1 g.). Much charring occurred but a brown oil (0·3 g.), b. p. 80—90°/2 mm., was obtained as distillate.

Present work				P. and H. (*loc. cit.*)			
$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε
2380	4·29	3260	3·58	2380	4·22	3260	3·48
2620	4·60	3380	3·70	2730	4·74	3360	3·58
2730	4·83	3510	2·96	2790	4·69	3410	3·64
2790	4·79	3610	2·16	2950	3·58	3510	3·18
2950	3·59					3610	2·34

Azulene. This brown oil was distilled, at 1 mm. pressure in an atmosphere of nitrogen, over palladium–charcoal (20%) heated to 350°. Deep blue needles of azulene formed in the receiver. The product was purified by fractionation on alumina, and its ultra-violet spectrum recorded. This coincided with that previously recorded by Plattner and Heilbronner (*Helv. Chim. Acta*, 1948, **31**, 804) (see the Table).

United College of St. Salvator and St. Leonard,
University of St. Andrews.

[*Received, July 15th*, 1953.]

---

757. *Constituents of the Higher Fungi. Part III.* Agrocybin.*

By E. R. H. Jones and J. D. Bu'Lock.

Since the characterisation of " Lachnophyllum ester " as methyl dec-2-en-4 : 6-diynoate (Wiljams, Smirnov, and Goljmov, *J. Gen. Chem. Russia*, 1935, **5**, 1195), the conjugated polyacetylenes have been shown to constitute a considerable group of natural products with a surprisingly wide distribution. Of outstanding importance has been the work of Sörensen and his collaborators on the isolation of a series of polyacetylenic compounds from plants of the Compositae family, where they are of widespread occurrence (cf. Sörensen, *Chem. and Ind.*, 1953, 240). Polyacetylene structures have also been established for the plant poisons, oenanthotoxin and cicutoxin (from Umbelliferae) (Anet, Lythgoe, Silk, and Trippett, *J.*, 1953, 309), and the component acids of certain seed oils (cf. Black and Weedon, *J.*, 1953, 1785). The occurrence of such compounds is not, however, confined to the higher plants, as polyacetylene compounds are also produced by certain fungi. A number of antibiotics isolated from various Basidiomycetes exhibit the characteristic ultra-violet absorption of poly-ynes; to those described by Anchell (*J. Amer. Chem. Soc.*, 1952, **74**, 1588) may be added two compounds from *Coprinus quadrifidus* (Doery, Gardner, Burton, and Abraham, *Antibiotics and Chemotherapy*, 1951, **1**, 409). Mycomycin, from the soil actinomycete *Nocardia acidophilus* and having the structure trideca-3 : 5 : 7 : 8-tetraen-10 : 12-diynoic acid (Celmer and Solomons, *J. Amer. Chem. Soc.*, 1952, **74**, 1860, 3838; 1953, **75**, 1372), has hitherto been the only polyacetylene antibiotic of known structure. In this paper we describe the characterisation of a second antibiotic, agrocybin, as octa-2 : 4 : 6-triynamide.

Through the courtesy of Dr. W. J. Robbins, Director of the New York Botanical Gardens, and Dr. M. Anchell, we were supplied with cultures of several fungi, on the metabolic products of which preliminary work had been done. From one of these, *Agrocybe dura*, Kavanagh, Hervey, and Robbins (*Proc. Nat. Acad. Sci.*, 1950, **36**, 102) had isolated an antibiotic, agrocybin, for which they reported details of biological activity and some physical properties, including the ultra-violet absorption spectrum. Using a process similar to theirs, we were able to isolate agrocybin from culture liquids in yields of *ca.* 30 mg./l., although not reproducibly.

Agrocybin formed crystals which decomposed explosively at 130—140° without

* Part II, *J.*, 1940, 1491.

melting, and blackened in a few hours when exposed to light. The ultra-violet absorption spectrum (see table) is characteristic of the chromophore ·$[C{:}C]_3$·R′, where R′ is a carboxyl

Agrocybin in ethanol [1]	$\lambda_{max.}$, Å	2150	2240	2690	2860	3040	3250
	10^{-3} ε	68·0	86·5	1·75	2·40	3·05	1·95
Octa-2 : 4 : 6-triynoic acid in ethanol [2] ...	$\lambda_{max.}$, Å	—	2200	2700	2860	3050	3260
	10^{-3} ε	—	62·0	2·4	2·8	2·5	2·1

[1] Positions of maxima agree with those previously reported by Kavanagh *et al.* (*loc. cit.*). [2] From Jones, Whiting, Armitage, Cook, and Entwistle, *Nature*, 1951, **168**, 900.

group or its spectroscopic equivalent. Comparison of the observed absorption intensities with the molecular-extinction coefficients for octa-2 : 4 : 6-triynoic acid indicated a molecular weight of *ca.* 150, assuming that agrocybin contains only one chromophore; on the same assumption, the hydrogenation equivalent gave a more accurate value of 135 ± 5. Analytical data (see Experimental) indicated the presence of one atom of nitrogen in a molecule of this size; this, coupled with the observation that agrocybin is a neutral compound, suggested that the chromophore might be ·$[C{:}C]_3$·CO·NH_2. (Other work in these laboratories, as yet unpublished, has shown that the absorption spectrum of hepta-2 : 4-diynoic acid closely resembles that of its amide.) This was confirmed by the infra-red absorption spectrum of the compound, measured in Nujol suspension, which shows bands at 2125 and 2210 cm.$^{-1}$, characteristic of a conjugated poly-yne, and at 1420, 1620, and 1680 cm.$^{-1}$, characteristic of a conjugated primary amide. The spectrum also showed that ethynyl groups were absent, so that a structure of the type R·$[C{:}C]_3$·CO·NH_2 was indicated. The nature of the non-chromophoric group R was established by the hydrogenation of agrocybin, which was rapid and quantitative, to give a compound identified by m. p., mixed m. p., and infra-red spectrum as octanamide. Thus agrocybin is octa-2 : 4 : 6-triynamide.

Agrocybin was not affected by contact with dilute aqueous alkali at 25°, but during 30 minutes of treatment with 1% potassium hydroxide in ethanol the optical density around 3000 Å increased about tenfold, the resulting solution having absorption maxima at 2850 (infl.), 2970, 3120, and 3270 Å (infl.) (relative intensities 0·8, 1·0, 1·0, 0·75). Changes of this type, which have been observed with other, similar, poly-ynes, are probably to be ascribed to a base-catalysed addition of ethanol to the conjugated poly-yne system, and are to be distinguished from the ready isomerisation, in aqueous alkali, of polyacetylenes containing an allene group (cf. Celmer and Solomons, *loc. cit.*). Studies of both types of reaction are in progress in these laboratories and will be reported in due course.

Experimental.—Isolation. Cultures of *A. dura* were grown on a corn-steep medium as described by Kavanagh *et al.* (*loc. cit.*). The culture liquid was extracted twice with 1/10 volume of ethyl acetate, the combined extracts evaporated to a small volume, the concentrate washed with 2% aqueous sodium hydrogen carbonate, and the ethyl acetate finally removed by evaporation over a small volume of water, all evaporations being carried out under reduced pressure. This procedure gave substantially pure agrocybin (yield, *ca.* 30 mg./l. of culture liquid). The product, recrystallised (to constant extinction coefficient) from aqueous ethanol, decomposed explosively at 130—140° [Found: C, 66·1; H, 3·9; N, 10·7; OMe, absent. C_8H_5ON requires C, 73·3; H, 3·8; N, 10·7%. Kavanagh *et al.* (*loc. cit.*) found C, 65·6; H, 4·3%; accurate analyses are frequently difficult to obtain with compounds of this type, particularly when, as in this case, only a limited amount of material is available].

Hydrogenation. Agrocybin (10·0 mg.), hydrogenated over Adams's platinum catalyst in ethanol, rapidly took up the calculated volume of hydrogen (Found: 11·2 c.c. at 22°/757 mm. C_8H_5ON, three triple bonds, requires 11·2 c.c.). The filtered solution was evaporated and the solid residue recrystallised from light petroleum to give octanamide, m. p. 103—105°, not depressed by admixture with authentic material, m. p. 105—106°, and depressed to 92—98° by admixture with nonanamide, m. p. 99°.

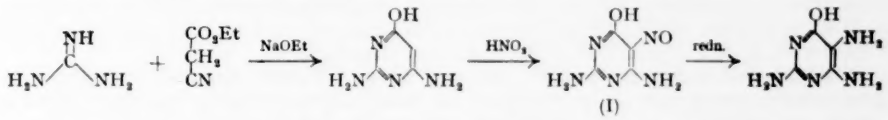
THE UNIVERSITY, MANCHESTER, 13.

[*Received, July 18th*, 1953.]

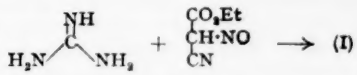
758. *A Convenient Synthesis of Some 4-Substituted 5-Aminopyrimidines.*

By Phyllis D. Landauer and H. N. Rydon.

5-Aminopyrimidines containing hydroxyl or amino-groups in the 4- or 6-positions have usually been prepared (cf. Lythgoe, *Quart. Reviews*, 1949, **3**, 181) by a three-stage process involving condensation of an active methylene compound with urea or a derivative, followed by nitrosation (or coupling with a diazonium salt) and reduction, *e.g.*, 2 : 4 : 5-triamino-6-hydroxypyrimidine was prepared as follows (Traube, *Ber.*, 1900, **33**, 1371) :



We now report work on a shorter route in which the intermediate nitroso-compound is prepared by direct condensation of the urea derivative with the readily available ethyl hydroxyiminocyanoacetate (Conrad and Schulze, *Ber.*, 1909, **42**, 735) or ethyl hydroxyiminomalonate (*iso*nitrosomalonate) (Cerchez, *Bull. Soc. chim.*, 1930, **47**, 1279), *e.g.* :



The condensation of ethyl hydroxyiminocyanoacetate with, *inter al.*, urea and guanidine is described in a German patent (D.R.P. 206453; "Friedländer," **9**, 1005) and that of ethyl hydroxyiminomalonate with thiourea by Johnson and Nicolet (*J. Amer. Chem. Soc.*, 1914, **36**, 354), but the possibilities of this method appear to have been overlooked by most workers in the pyrimidine field.

The method is very simple and convenient, and gives overall yields which are often superior to those obtained by using the more usual procedure; the method is especially valuable for the preparation of 2 : 4 : 5-triamino-6-hydroxypyrimidine, a key intermediate in the preparation of pteroic and folic acids. In the initial condensation with the hydroxyimino-compound either one or two equivalents of sodium ethoxide are used, the choice depending on the relative solubilities of the resulting 5-nitrosopyrimidine and its sodium salts; in certain cases we have found efficient stirring to be essential. The reduction of the 5-nitrosopyrimidine to the amino-compound can be conveniently effected by using either sodium hydrosulphite (dithionite) or Raney nickel; the former is convenient in cases when the 5-aminopyrimidine can be isolated as an insoluble sulphate but the latter is preferable in cases where the sulphate of the product is freely soluble in water or where it is desired to eliminate a thiol group simultaneously with the reduction. We outline below satisfactory procedures for the preparation of 2 : 4 : 5-triamino-6-hydroxy-, 4 : 5-diamino-6-hydroxy-2-methyl-, 4 : 5-diamino-6-hydroxy-, 4 : 5-diamino-2 : 6-dihydroxy-, and 2 : 5-diamino-4 : 6-dihydroxy-pyrimidine (divicine).

Experimental.—*2 : 4 : 5-Triamino-6-hydroxypyrimidine.* Finely powdered guanidine hydrochloride (19·1 g., 0·2 mole) was added to ethanolic sodium ethoxide, prepared from sodium (9·1 g., 0·4 mole) and ethanol (125 ml.). After 30 min. at room temperature with occasional shaking, sodium chloride was filtered off and ethyl hydroxyiminocyanoacetate (28·4 g., 0·2 mole) added to the filtrate; the mixture was shaken vigorously and then kept at room temperature overnight. The precipitated 2 : 4-diamino-6-hydroxy-5-nitrosopyrimidine (I) was filtered off, washed with water, and suspended in hot water (750 ml.); sodium dithionite (40 g.) was added and the mixture boiled for 5 min., the red colour of the nitroso-compound being discharged. Slow addition of concentrated sulphuric acid (180 ml.) precipitated 2 : 4 : 5-triamino-6-hydroxypyrimidine sulphate, which was filtered off after cooling (29·0 g.;

59%); it crystallised from 2N-sulphuric acid in needles (Found: N, 28·1, 28·2. Calc. for $C_4H_7ON_5,H_2SO_4,\frac{1}{2}H_2O$: N, 28·2%).

4 : 5-*Diamino*-6-*hydroxy*-2-*methylpyrimidine*.—Acetamidine hydrochloride (9·45 g., 0·1 mole) was condensed as usual with ethyl hydroxyiminocyanoacetate (14·2 g., 0·2 mole) by using sodium ethoxide from sodium (4·6 g., 0·2 mole) and ethanol (100 ml.). The pale violet sodium salt of 4-amino-6-hydroxy-2-methyl-5-nitrosopyrimidine (14 g., 79%) was filtered off, washed with a little ethanol, and dried at 100°. On a larger scale it was essential to add the hydroxyimino-ester with efficient mechanical stirring. This salt (4·4 g.) was dissolved in water (100 ml.), and the solution warmed to 70°; wet Raney nickel catalyst was added in portions until no further colour change occurred. The mixture was then heated on the steam-bath for an hour, and the nickel filtered off and washed thoroughly with hot water. The filtrate and washings were acidified with sulphuric acid and concentrated under reduced pressure to 50 ml. Basification with ammonia solution precipitated **4 : 5**-diamino-6-hydroxy-2-methylpyrimidine in sparkling platelets (2·5 g., 72%); recrystallisation from 2N-sulphuric acid gave the sulphate in needles, m. p. 265° (Found: N, 23·6. Calc. for $C_5H_8ON_4,H_2SO_4$: N, 23·5%).

4 : 5-*Diamino*-6-*hydroxypyrimidine*. Thiourea (38 g., 0·5 mole) was condensed with ethyl hydroxyiminocyanoacetate (71 g., 0·5 mole), by using sodium ethoxide, from sodium (23 g., 1 mole) and ethanol (1 l.). The brown-red sodium salt of 4-amino-6-hydroxy-2-mercapto-5-nitrosopyrimidine (75 g., 77%) was filtered off, washed with a little ethanol, and dried at 100°. This salt (4·9 g.) was reduced with Raney nickel as described for the 2-methyl compound; the concentrate, after being kept at 0° overnight, deposited **4 : 5**-diamino-6-hydroxypyrimidine (2·0 g., 63%) which yielded the hemisulphate as needles, m. p. 268°, on crystallisation from 2N-sulphuric acid (Found: N, 31·6; S, 9·0. Calc. for $C_4H_6ON_4,\frac{1}{2}H_2SO_4$: N, 32·0; S, 9·2%).

4 : 5-*Diamino*-2 : 6-*dihydroxypyrimidine*. Urea (6·0 g., 0·1 mole) was condensed with ethyl hydroxyiminocyanoacetate (14·2 g., 0·1 mole) and sodium ethoxide, from sodium (4·6 g., 0·2 mole) and ethanol (150 ml.). The precipitated nitroso-compound was filtered off and suspended in 4% sodium hydroxide solution (400 ml.) at 60°; sodium dithionite was added in small portions until the solution was clear and no further colour change occurred. The solution was boiled with charcoal, filtered, cooled to room temperature, and treated with concentrated sulphuric acid (25 ml.); the precipitated **4 : 5**-diamino-2 : 6-dihydroxypyrimidine sulphate was filtered off and recrystallised from 2N-sulphuric acid; the yield was 11 g. (46%).

2 : 5-*Diamino*-4 : 6-*dihydroxypyrimidine* (*divicine*). Guanidine hydrochloride (9·55 g., 0·1 mole) was added to sodium ethoxide, from sodium (6·9 g., 0·3 mole) and ethanol (150 ml.). After 30 min. at room temperature, the mixture was refluxed while ethyl hydroxyiminomalonate was added during 10 min. with rapid mechanical stirring; refluxing and stirring were continued for a further hour. The precipitated nitroso-compound was filtered off, suspended in water (400 ml.) at 60°, and reduced, as described above, with sodium dithionite. Concentrated sulphuric acid (25 ml.) was added to the cooled solution, and the precipitated divicine hemisulphate was filtered off, washed, and dried (8·6 g., 45%).

The sulphate (1·45 g.) was triturated with water (10 ml.), and 2N-sodium hydroxide (4 ml.) added dropwise to bring the pH to 8. The base was filtered off and at once warmed with N-hydrochloric acid (30 ml.); after the solution had been filtered, while hot, from a little sulphate, ethanol (30 ml.) was added, followed by sufficient water (10 ml.) to re-dissolve the precipitated hydrochloride. The solution was boiled with charcoal, filtered, and more ethanol (40 ml.) added to the hot filtrate. Divicine hydrochloride (1·03 g., 69%) crystallised in beautiful flattened needles. Recrystallisation from 2N-hydrochloric acid (25 ml.) and ethanol (25 ml.) gave analytically pure material (0·73 g.) (Found: N, 28·5; Cl, 18·1. Calc. for $C_4H_6O_2N_4,HCl,H_2O$: N, 28·5; Cl, 18·1%).

We are grateful to Messrs. H. G. Baxter and R. H. Doust for experimental assistance and to the Department of Scientific and Industrial Research for a Maintenance Allowance (to P. D. L.). Analyses were carried out in the microanalytical laboratory (Mr. F. H. Oliver) of this Department.

Department of Organic Chemistry,
Imperial College of Science and Technology,
London, S.W.7.

[*Received, July 18th,* 1953.]

759. *Methanesulphonic Anhydride.*

By L. N. Owen and S. P. Whitelaw.

For the synthesis of certain types of methanesulphonates the use of methanesulphonic anhydride, rather than the chloride, may be advantageous (compare Linstead, Owen, and Webb, *J.*, 1953, 1225). The only method so far described for the preparation of the anhydride involves the interaction of silver methanesulphonate with methanesulphonyl chloride (Billeter, *Ber.*, 1905, **38**, 2018). Aromatic sulphonic anhydrides have been obtained by reaction of a sulphonic acid, or its sodium salt, with thionyl chloride (Meyer and Schlegl, *Monatsh.*, 1913, **34**, 561; Meyer, *Annalen*, 1923, **433**, 335; Fichter and Stocker, *Helv. Chim. Acta*, 1924, **7**, 1072), but such methods have not been applied to aliphatic sulphonic acids. We have now found that methanesulphonic anhydride can be simply prepared in over 80% yield by treatment of methanesulphonic acid with boiling thionyl chloride.

Experimental.—Methanesulphonic acid (35 g.), b. p. 140°/2 mm., and thionyl chloride (100 c.c.) were boiled under reflux for 3 hr., and then evaporated to a dark solid residue which was extracted with boiling dry ether. Evaporation of the extracts gave the crude anhydride, which after recrystallisation from dry ether formed prisms (26 g., 82%), m. p. 70—71° (Billeter, *loc. cit.*, gives m. p. 71°).

Poor yields of anhydride (<20%) were obtained by reaction of (i) sodium methanesulphonate with boiling thionyl chloride, (ii) methanesulphonic acid or its sodium salt with methanesulphonyl chloride at 160°, (iii) methanesulphonyl chloride (2 mol.) and water (1 mol.) at 160°.

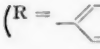
Department of Organic Chemistry, Imperial College of Science and Technology, South Kensington, London, S.W.7. [*Received, July 22nd,* 1953.]

---

760. *The Condensation of Glyoxal and* iso*Nicotinoylhydrazine (Isoniazid).*

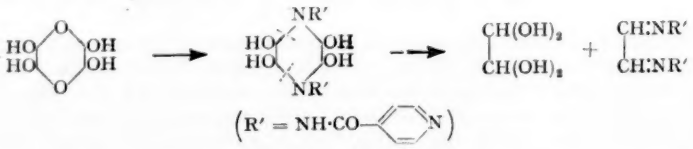
By Vincent C. Barry and P. W. D. Mitchell.

Isoniazid condenses with a variety of aldehydes and ketones to give crystalline hydrazones, many of which have been prepared for evaluation of their activity against *Mycobacterium tuberculosis* (Offe, Siefken, and Domagk, *Z. Naturforsch.*, 1952, **76**, 462; Yale, Losee, Martins, Holsing, Perry, and Bernstein, *J. Amer. Chem. Soc.*, 1953, **75**, 1933). With glyoxal the nature of its condensation product has been found to depend on the concentration of the solutions (Table 2). Thus when glyoxal (0·0086 mole) and isoniazid (0·022 mole) were condensed in 25 c.c. of water, the product was the monohydrazone (I), while the same quantities of reactants in 400 c.c. of water gave the bis-

(I) R·CO·NH·N:CH·CHO $\left(R = \text{  }\right)$ $(R\cdot CO\cdot NH\cdot N{:}CH\cdot)_2$ (II)

hydrazone (II). Both compounds were obtained as crystalline solids melting above 360°. The bishydrazone is insoluble in water and organic solvents but may be recrystallised from 50% aqueous acetic acid. Attempts at recrystallising the monohydrazone, which is slightly soluble in water and ethanol always yielded the bis-compound. The conversion of (I) into (II) can also be readily effected by 5 min.' boiling in 50% acetic acid or by dissolution at room temperature in dilute aqueous sodium hydroxide or in dilute mineral acids. Formation of the bishydrazone, in this way, was found to be accompanied by the liberation of glyoxal. In order to explain this reaction, it is suggested that the mono-

hydrazone arises from condensation of isoniazid with the dimeric form of glyoxal to give a dimeric monohydrazone which could then undergo cleavage, as shown, with the formation of the bishydrazone and glyoxal.



The *p*-nitrophenylhydrazone from 1-hydroxydioxan has been shown by Summerbell and Rochen (*J. Amer. Chem. Soc.*, 1941, **63**, 3241), to give glyoxal bis-*p*-nitrophenylhydrazone when refluxed with 25% aqueous acetic acid for 4 hr. In this case the authors suggested that the reaction proceeded by an autoxidation process.

The products obtained from glyoxal and isoniazid were identified by means of ultra-violet light-absorption measurements. In 0·1N-hydrochloric acid, the bishydrazone has a maximum at 267 mμ which moves to a higher wave-length in alkali. Thus in 0·1N-sodium hydroxide the yellow solution has a maximum at 366 mμ. These two maxima are probably those of the tautomeric forms of the bishydrazone, $(\cdot CH{:}N\cdot NH\cdot COR)_2 \rightleftharpoons (\cdot CH{:}N\cdot N{:}CR\cdot OH)_2$ (R as above). The monohydrazone in 0·1N-sodium hydroxide gives a yellow solution, having an absorption maximum at 366 mμ. The value of $E_{1\,cm.}^{1\%}$ corresponded well with that expected from a solution in which two molecules of the monohydrazone had given one of the bishydrazone. Measurements were also made on the hydrochloride and sulphate of (II) which are obtained when the monohydrazone is crystallised from dilute hydrochloric and sulphuric acid respectively. The molecular weights of these salts were confirmed by titration with alkali.

Experimental.—Glyoxal monoisonicotinoylhydrazone (I). An excess of 50% aqueous syrupy glyoxal was added to a concentrated aqueous solution of isoniazid. The solution immediately became yellow and after a few minutes a yellow precipitate was formed. This was washed with water, ethanol, and ether and dried in the vacuum-oven at 100° (P_2O_5). The cream-yellow *hydrazone* had m. p. >360° (Found: C, 54·2; H, 4·4; N, 23·2. $C_8H_7O_2N_3$ requires C, 54·2; H, 4·0; N, 23·8%).

Glyoxal bisisonicotinoylhydrazone (II). Dilute aqueous solutions (less than 1%) of glyoxal and isoniazid were mixed and kept overnight; the solution yielded well-defined colourless crystals of the hydrazone, m. p. >360° (Found: C, 56·3; H, 4·3; N, 27·9. Calc. for $C_{14}H_{12}O_2N_6$: C, 56·7; H, 4·1; N, 28·4%).

Conversion of (I) *into* (II). (*a*) The monohydrazone was boiled for 5 min. with 50% acetic acid. The pale yellow solution, on cooling, gave colourless rectangular plates, m. p. >360° (Found: C, 56·3; H, 4·4; N, 27·6%).

(*b*) A saturated solution of (I) in hot 0·1N-sodium hydroxide, on cooling, gave deep yellow crystals [presumably the *lactim* form of (II)], m. p. 329—331° (Found: C, 56·3; H, 4·2; N, 27·4%).

(*c*) A solution of (I) in hot dilute hydrochloric acid gave on cooling deep yellow crystals of the *hydrochloride*, m. p. >360° (Found: equiv., 188·7. $C_{14}H_{12}O_2N_6,2HCl$ requires equiv., 184·5). The *sulphate* (Found: equiv., 122·5. $C_{14}H_{12}O_2N_6,2H_2SO_4$ requires equiv., 123) was prepared in a similar way from dilute sulphuric acid and had m. p. 323° (decomp.). Both the hydrochloride and the sulphate were washed with ethanol and ether only, since they dissociate readily in water.

The salts (50 mg.), suspended in water (20 c.c.), were titrated with N/30-sodium hydroxide to chlorophenol-red.

Ultra-violet light absorption. The compounds described above (30 mg.) were dissolved in 0·1N-sodium hydroxide (10 c.c.) and diluted to 250 c.c. with water, and 10 c.c. of this solution diluted to 250 c.c. with 0·1N-sodium hydroxide. Extinctions were measured in 1·0-cm. cells with a Beckman photo-electric spectrophotometer (Model DU). The highest value of $E_{1\,cm.}^{1\%}$ obtained (1128) was, as expected, that of the bishydrazone (II). This value was used in calculations of the molecular weights of the other compounds (Table 1).

The values of $E^{1\%}_{1\,cm.}$ at 366 mμ given for the mono- and the bis-hydrazone in 0·1N-sodium hydroxide were used to disclose the nature of the products obtained when glyoxal and isoniazid were allowed to react at ordinary temperatures (see Table 2).

TABLE 1.

Substance	$E^{1\%}_{1\,cm.}$ at 366 mμ	Molecular weight: Required	Molecular weight: Calc. from u.-v. data
(II), m. p. >360°	1128	296	—
(II), m. p. 329°	1120	296	300
(II), hydrochloride	906	369	368
(II) sulphate	693	496	482
(I)	929	354	359

TABLE 2.

Glyoxal (g.) [a]	Isoniazid (g.)	H_2O (c.c.)	Yield (g.) after (*t*) hr.	$E^{1\%}_{1\,cm.}$	Comment
1	3	25	2·38 [a] (½)	892	Mono-
1	3	400	2·69 (2½)	1074	Mainly bis-
			0·91 [b] (18)	860	Mono-
0·5	3	25	1·93 (48)	968	Mainly mono-
0·5	3	400	1·53 (24)	1060	Mainly bis-
0·5	0·5	400	0·31 (24)	1035	Mixture

[a] 1 g., boiled with 50% acetic acid (40 c.c.) for 5 min., gave the bishydrazone (0·82 g.; $E^{1\%}_{1\,cm.}$ at 366 mμ = 1069; calcd. yield, 0·84 g.). The filtrate from this experiment contained glyoxal since the bishydrazone (0·25 g.; $E^{1\%}_{1\,cm.}$ at 366 mμ = 1110) was obtained on addition of isoniazid (1 g.). [b] This was a second crop of crystals separating from the filtrate after 18 hr. 300 mg., when boiled with ethanol (300 c.c.), gave the bishydrazone (160 mg.; $E^{1\%}_{1\,cm.}$ at 366 mμ = 1153). The filtrate, on evaporation to dryness, gave a yellow residue (137 mg.), readily soluble in water. The solution (25 c.c.), on addition of isoniazid (0·7 g.), yielded the bishydrazone of glyoxal (72 mg.; $E^{1\%}_{1\,cm.}$ at 366 mμ = 1126). [c] Solid polymer separating from 50% aqueous solution.

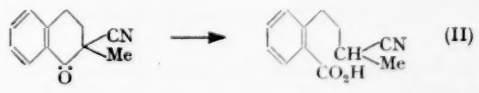
One of us (P. W. D. M.) is indebted to University College, Dublin, for a Lasdon Foundation Research Fellowship.

LABORATORIES OF THE MEDICAL RESEARCH COUNCIL OF IRELAND,
TRINITY COLLEGE, DUBLIN. [*Received, July 29th*, 1953.]

761. *Ring Fission of 2-Cyano-1 : 2 : 3 : 4-tetrahydro-2-methyl-1-oxonaphthalene.*

By D. B. COWELL, W. H. LINNELL, and D. W. MATHIESON.

DURING attempts to condense 2-cyano-1 : 2 : 3 : 4-tetrahydro-2-methyl-1-oxonaphthalene (I) with diethyl or dimethyl succinate in presence of potassium *tert.*-butoxide, the only product isolated under a large variety of conditions was diethyl or dimethyl 2 : 5-dioxo-*cyclo*hexane-1 : 4-dicarboxylate. None of the expected tricyclic ketones was formed and no starting material was recoverable. Under the conditions normally used for such



condensations the main reaction in this case appears to be ring fission (cf. Johnson, Petersen, and Gutsche, *J. Amer. Chem. Soc.*, 1947, **69**, 2942). Thus it has been found that when the cyano-ketone (I) is treated with potassium *tert.*-butoxide alone, even under relatively mild conditions (55°; 5 hr.), cleavage of the alicyclic ring takes place with formation of

the cyano-acid (II). The structure of (II) was confirmed by hydrolysis to the dicarboxylic acid, followed by ring closure to 1 : 2 ; 3 : 4-tetrahydro-2-methyl-1-oxonaphthalene.

Experimental.—*2-Cyano-*1 : 2 : 3 : 4*-tetrahydro-2-methyl-*1*-oxonaphthalene.* This *ketone* was obtained (85% yield) from 2-cyano-1 : 2 : 3 : 4-tetrahydro-1-oxonaphthalene by a route similar to that described by Johnson, Petersen, and Gutsche (*J. Amer. Chem. Soc.*, 1947, **69**, 2942) for the corresponding tetrahydro-oxophenanthrene, and had b. p. 128°/1 mm., m. p. 28° (Found : C, 77·6; H, 5·6; N, 7·6. $C_{12}H_{11}ON$ requires C, 77·8; H, 5·9; N, 7·6%).

γ-o-Carboxyphenyl-α-methylbutyronitrile (II). The above cyano-ketone (1·87 g.) was heated for 5 hr. at 55° with potassium (2 g.) in *tert.*-butyl alcohol (50 ml.). After addition of water and removal of solvent the residue was extracted with sodium carbonate. The *acid* fraction (1·48 g.) had b. p. 144—146°/0·06 mm., m. p. 42—45° (Found : C, 71·0; H, 6·5; N, 6·6. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·5; N, 6·9%).

Hydrolysis of the cyano-acid with 30% sulphuric acid for 10 hr. gave *γ-o-carboxyphenyl-α-methylbutyric acid*, crystallising from aqueous acetic acid in needles, m. p. 133—134° (Found : C, 65·6; H, 6·1. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·4%).

1 : 2 : 3 : 4*-Tetrahydro-2-methyl-*1*-oxonaphthalene.* The dicarboxylic acid (0·25 g.) was refluxed for 8 hr. with acetic anhydride, and the residue obtained after removal of the reagent was heated at 250°/4 mm. until no further carbon dioxide was evolved. On addition of Brady's reagent to the residue the 2 : 4*-dinitrophenylhydrazone* of the ketone was obtained, crystallising from dioxan–alcohol in prisms, m. p. 235—236° (Found : C, 59·9; H, 4·8; N, 16·6. $C_{17}H_{16}O_4N_4$ requires C, 60·0; H, 4·7; N, 16·5%). This gave no m. p. depression on admixture with a sample prepared from an authentic specimen of 1 : 2 : 3 : 4-tetrahydro-2-methyl-1-oxonaphthalene (Sah and Brüll, *Ber.*, 1940, **73**, 1430). The ultra-violet absorption characteristics of both samples were identical, *viz.*, $\lambda_{max.}$ 390 mμ (ε 29,000) (main band only, in $CHCl_3$).

One of us (D. W. M.) thanks the University of London for the award of an I.C.I. Fellowship.

School of Pharmacy, London University,
17, Bloomsbury Square, London, W.C.1. [*Received, August 5th,* 1953.]

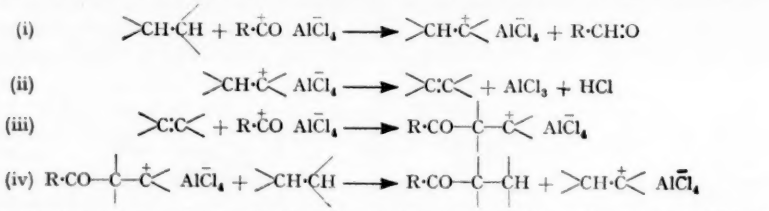
---

762. *Transfer of Hydride Ion.*

By G. Baddeley and W. Pickles.

*iso*Propyl bromide, *iso*propyl alcohol, and di*iso*propyl ether are decomposed by aluminium chloride at room temperature and evolve propane; decomposition of diethyl ether with evolution of ethane requires higher temperatures. These reactions are related on the one hand to the alkylation and acylation of aliphatic hydrocarbons and on the other to the acid-catalysed conversion of alcohols and ethers into hydrocarbon and carbonyl compound. It is suggested that *all* these reactions are effected by transfer of hydride ion.

Transfer of hydride ion is fundamental in the alkylation and acylation of aliphatic and alicyclic hydrocarbons by the Friedel–Crafts method (Schmerling, " Catalytic Re-



actions of Hydrocarbons—Ionic Mechanism," Symposium No. 24, Sept., 1952, New Jersey; Bartlett, Condon, and Schneider, *J. Amer. Chem. Soc.*, 1944, **66**, 1531; Baddeley, Wrench, and Williamson, *J.*, 1953, 2110); for example, acylation, the simpler process, involves at least a chain-initiating reaction (i) and a chain reaction (ii)—(iii)—(iv), of which (i) and (iv) are effected by transfer of hydride ion. A similar scheme with acyl replaced by alkyl cation represents some of the reactions occurring in the alkylation process.

Mixtures of aluminium chloride and alkyl halide, alcohol, ether, or olefin, and hydrogen halide are frequently used for the nuclear alkylation of aromatic compounds, but when these are not readily alkylated, *e.g.*, aryl ketones (*J.*, 1949, S229), or when they are absent the alkylating agent extracts hydride ion from an aliphatic side-chain (unpublished observation) or from the compound providing the alkylating agent. The latter reaction was first reported by Friedel and Crafts (*Ann. Chim.*, 1884, **1**, 451) : they obtained hydrogen chloride and a mixture of *saturated* hydrocarbons from *iso*amyl and aluminium chlorides. We find that *iso*propyl bromide, with catalytic amounts of reagent, evolves propane (0·5 mol.) and hydrogen halide (cf., Meyer, *Ber.*, 1894, **27**, 2766); the reaction is given the following tentative inperpretation :

$$Me_2CHX + AlX_3 \longrightarrow Me_2\overset{+}{C}H\ Al\overset{-}{X}_4$$

$$Me_2C(X)\text{–}H \rightarrow \overset{+}{C}HMe_2\ Al\overset{-}{X}_4 \longrightarrow Me_2\overset{+}{C}X\ Al\overset{-}{X}_4 + Me_2CH_2$$

$$Me_2\overset{+}{C}X\ Al\overset{-}{X}_4 \longrightarrow HX + AlX_3 + CH_2{:}CMeX \longrightarrow \text{Polymer}$$

This type of reaction occurs less readily with ethyl bromide since this, probably, loses hydride ion less readily than does *iso*propyl bromide; this view is supported by the fact that, in the presence of aluminium chloride, nitrobenzene is reduced by *iso*propyl but not by ethyl bromide (Gilman, Burtner, Calloway, and Turck, *J. Amer. Chem. Soc.*, 1935, **57**, 907).

Whereas *iso*propyl alcohol affords the chloride on addition of a molecular proportion of reagent (formulated as $AlCl_3$), reaction (v) (Norris and Sturgis, *ibid.*, 1939, **61**, 1413), we find that, even at room temperature, excess of reagent provides propane. Since ketones are also formed, the reaction is formulated as in (vi) and (vii). Di*iso*propyl ether also reacts at room temperature with evolution of propane; the reaction is suitably represented by (viii) followed by (vi) and (vii). Similarly, diethyl ether evolves ethane but reaction occurs only on warming (90—100°).

(v) $Me_2CH{\cdot}OH + AlCl_3 \longrightarrow Me_2CH{\cdot}OH,AlCl_3 \longrightarrow HCl + Me_2CH{\cdot}O{\cdot}AlCl_2 \longrightarrow Me_2CHCl + AlOCl$

(vi) $$Me_2C(OAlCl_2)\text{–}H \rightarrow \overset{+}{C}HMe_2\ Al\overset{-}{Cl}_4 \longrightarrow Me_2\overset{+}{C}OAlCl_2\ Al\overset{-}{Cl}_4 + Me_2CH_2$$

(vii) $$Me_2\overset{+}{C}{\cdot}O{\cdot}AlCl_2\ Al\overset{-}{Cl}_4 \longrightarrow Me_2C{:}O,AlCl_3 + AlCl_3$$

$$\downarrow$$

Condensation products

(viii) $$(Me_2CH)_2O,AlCl_3 \longrightarrow Me_2CH{\cdot}O{\cdot}AlCl_2 + Me_2CHCl$$

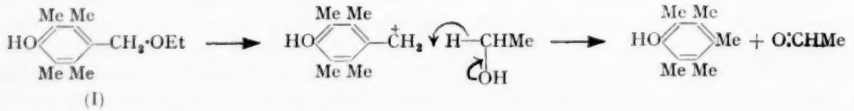
Decomposition of ethers and alcohols into hydrocarbon and carbonyl compound has often been described and, when catalysed by acid, is, in our opinion, closely related to the above observations and best represented by the general expression :

$$R'R''CH{\cdot}OR \underset{}{\overset{H^+}{\rightleftharpoons}} R'R''C(OH)\text{–}H \rightarrow \overset{+}{R} \xrightarrow{-H^+} R'R''C{:}O + RH$$

$$R'R''CH{\cdot}OH + ROH \xrightarrow[-H_2O]{H^+} R'R''C(OH)\text{–}H \rightarrow \overset{+}{R}$$

It relates the reaction to the Cannizzaro reaction, incorporates the fact that alkylating agent is formed (for numerous illustrations see Price " The Alkylation of Aromatic Compounds by the Friedel–Crafts Method," Organic Reactions, Vol. III), and implies that rate of reaction is directly related to the ease with which hydride ion is released by the alcohol R'R''CH·OH. This implication is readily substantiated; for example, since ethyl alcohol is a more powerful reducing agent than methyl alcohol, alkyl and aralkyl cations should be more readily reduced to hydrocarbon in the former alcohol. This is the case; 4-ethoxy-

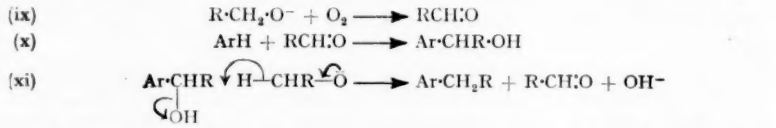
methyltetramethylphenol (I) provides pentamethylphenol and acetaldehyde in ethanolic hydrogen chloride but is not reduced when methanol is used (Burawoy and Chamberlain, *J.*, 1949, 626):



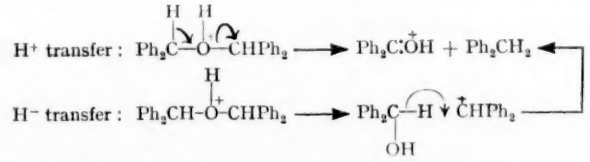
(I)

Similarly, tri- and di-phenylmethanol are reduced to the corresponding methane derivatives by mineral acid and ethyl alcohol, and triphenylmethyl chloride, in diethyl ether, is reduced in the presence of zinc chloride or aluminium chloride (Norris and Young, *J. Amer. Chem. Soc.*, 1924, **46**, 2580).

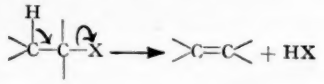
Transfer of hydride ion is a recognised feature of termination of chain-reaction in acid-catalysed polymerisation of olefins, of many oxidation reduction processes, *e.g.*, reduction of ketones with aluminium alkoxide, and of alkylation with alkoxide ion (Cornforth, Cornforth, and Robinson, *J.*, 1942, 682). In the last instance, the mechanism of reaction provided by the authors can be represented by (ix)—(x)—(xi); (ix) initiates the chain reaction (x)—(xi).



Some of the above oxidation–reduction processes can be formulated as though hydrogen is transferred as proton instead of as hydride ion; this is illustrated by the *acid*-catalysed conversion of bisdiphenylmethyl ether into benzophenone and diphenylmethane:

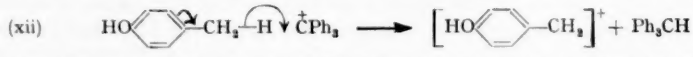


These formulations may represent alternative mechanisms and we plan to provide data which will distinguish between them; *e.g.*, the latter requires that this reaction, like the Cannizzaro reaction (Fredenhagen and Bonhoeffer, *Z. physikal. Chem.*, 1938, *A*, **181**, 379), should occur without exchange of hydrogen between organic reactant and hydroxylic solvent. Burton and Cheeseman (*J.*, 1953, 986) prefer the former since it resembles the well-known elimination reactions:



Transfer of hydride ion sometimes obstructs or competes with aromatic substitution. We conclude with a few examples.

(*a*) Whereas *o*-cresol is alkylated by triphenylmethanol in acetic–sulphuric acid, *p*-cresol reduces the alcohol to the corresponding methane and is oxidised to "polymerised



quinomethane" (Boyd and Hardy, *J.*, 1928, 630; Schorigin, *Ber.*, 1927, **60**, 2373). The reaction is now represented by (xii); the 4-hydroxybenzyl cation combines with phenolic material, as in the preparation of phenol–formaldehyde resins.

(*b*) Benzoyl cation oxidises 9 : 10-dihydroanthracene to anthracene; this gives the 9-benzoyl derivative which is reduced by dihydroanthracene to the final product, 9-benzoyl-9 : 10-dihydroanthracene (Nenitzescu, Gavăt, and Cocora, *Ber.*, 1939, **72**, 819; Baddeley, Wrench, and Williamson, *loc. cit.*).

(*c*) Acetyl cation oxidises 5-acetylindane and 6-acetyltetralin to the corresponding indene and 1 : 2-dihydronaphthalene derivatives, and these are acetylated (Baddeley, Wrench, and Williamson, *loc. cit.*).

(*d*) Alkylation of benzene by diphenylmethyl chloride and aluminium chloride provides mainly diphenylmethane and triphenylmethyl chloride (Boesekin, *Rec. Trav. chim.*, 1903, **22**, 311). Triphenylmethane is formed but, by losing hydride ion to the diphenylmethyl cation, forms the more stable triphenylmethyl cation which does not readily attack benzene.

$$PhH + Ph_2\overset{+}{C}H\ Al\bar{C}l_4 \longrightarrow Ph_3CH + HCl + AlCl_3$$

$$Ph_3CH + Ph_2\overset{+}{C}H\ Al\bar{C}l_4 \longrightarrow Ph_3\overset{+}{C}\ Al\bar{C}l_4 + Ph_2CH_2$$

A full account of the reactions which are reported for the first time in this paper will form part of a later communication.

We thank Mr. C. E. Spooner for a number of gas analyses.

FACULTY OF TECHNOLOGY, UNIVERSITY OF MANCHESTER. [*Received, August 6th*, 1953.]

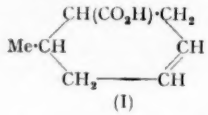
OBITUARY NOTICE.

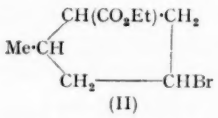
EDWARD HOPE.

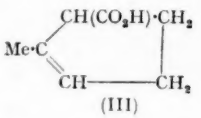
1886—1953.

EDWARD HOPE was born on December 19th, 1886, at Lowton, Lancashire, and died on February 7th, 1953, at Caterham, Surrey. He was educated at Leigh Grammar School and Manchester University, where he received his chemical training under W. H. Perkin, jun.

Some of his early researches were with problems which had a direct bearing on the work of Perkin and his school on the synthesis of terpenes. In a study of some applications of the Michael reaction (*J.*, 1911, **99**, 762) ethyl crotonate was treated with ethyl sodiocyanoacetate and the product condensed with ethyl bromoacetate with the formation of ethyl 2-cyano-3-methylbutane-1 : 2 : 4-tricarboxylate, which, on hydrolysis and decarboxylation, gave 3-methylbutane-1 : 2 : 4-tricarboxylic acid, $CO_2H{\cdot}CH_2{\cdot}CH(CO_2H){\cdot}CHMe{\cdot}CH_2{\cdot}CO_2H$, identical with an acid obtained by Perkin (*J.*, 1911, **99**, 743) by the oxidation of 6-methyl*cyclo*hex-3-enecarboxylic acid (I). Treatment of the ethyl ester of this tribasic acid with sodium, and hydrolysis of the product, led to 2-methyl-4-oxo*cyclo*pentanecarboxylic acid, from which, by reduction to the alcohol, conversion into the corresponding bromide, and subsequent esterification, the compound (II) was obtained. When this ester was heated with diethylaniline and then hydrolysed, the product was mainly a mixture of 2-methyl*cyclo*pent-3- and -4-enecarboxylic acids as expected, but a small amount of 2-methyl*cyclo*pent-2-enecarboxylic acid (III) was also present as the result of an isomeric change. Pentane-1 : 2 : 4-tricarboxylic acid, $CO_2H{\cdot}CH_2{\cdot}CH(CO_2H){\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H$, was obtained similarly from ethyl methylacrylate, $CH_2{:}CMe{\cdot}CO_2Et$, and converted into 3-methyl-4-oxo*cyclo*pentanecarboxylic acid.

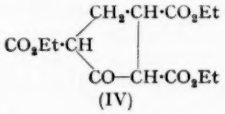

(I)


(II)


(III)

The condensation of ethyl citraconate, $CO_2Et{\cdot}CMe{:}CH{\cdot}CO_2Et$, with ethyl sodiomalonate was investigated in the light of work by Michael and his collaborators. Contrary to earlier belief, the reaction in ether or benzene gave ethyl butane-1 : 1 : 2 : 3-tetracarboxylate, $(CO_2Et)_2CH{\cdot}CH(CO_2Et){\cdot}CHMe{\cdot}CO_2Et$. In cold alcohol, ethyl butane-1 : 2 : 4 : 4-tetracarboxylate, $CO_2Et{\cdot}CH_2{\cdot}CH(CO_2Et){\cdot}CH_2{\cdot}CH(CO_2Et)_2$, was obtained, apparently through change of the citraconate into ethyl itaconate, $CH_2{:}C(CO_2Et){\cdot}CH_2{\cdot}CO_2Et$. This substance is no doubt an intermediate in the formation, at a higher temperature, of the compound, $C_{14}H_{20}O_7$, which Michael (*Ber.*, 1900, **33**, 3758) had regarded as a *cyclo*butane derivative, but Hope (*J.*, 1912, **101**, 892) showed to be ethyl 3-oxo*cyclo*pentane-1 : 2 : 4-tricarboxylate (IV).

Further studies (*J.*, 1922, **2223**) included the action of hydrogen cyanide, particularly in aqueous alcohol in the presence of potassium cyanide (compare Lapworth, *J.*, 1903, **83**, 995), on ethyl α-cyano-β-methylglutaconate, $CO_2Et{\cdot}CH(CN){\cdot}CMe{:}CH{\cdot}CO_2Et$, and its two methyl derivatives (V) and (VI). The first-named gave ethyl αβ-dicyano-β-methylglutarate, from which β-methyltricarballylic acid, $CO_2H{\cdot}CH_2{\cdot}CMe(CO_2H){\cdot}CH_2{\cdot}CO_2H$, was obtained on hydrolysis (*J.*, 1912, **101**, 892), while the esters (V) and (VI) both gave ethyl 1 : 2-dicyano-2-methylbutane-1 : 3-dicarboxylate, $CO_2Et{\cdot}CH(CN){\cdot}CMe(CN){\cdot}CHMe{\cdot}CO_2Et$, from which αβ-di-methyl- and αβγ-trimethyl-tricarballylic acid were prepared.

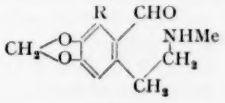

(IV)

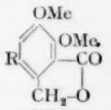
$CO_2Et{\cdot}C(CN){:}CMe{\cdot}CHMe{\cdot}CO_2Et$ (V)

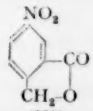
$CO_2Et{\cdot}CH(CN){\cdot}CMe{:}CMe{\cdot}CO_2Et$ (VI)

While in Manchester Hope collaborated with Sir Robert Robinson in some notable investigations into the synthesis of alkaloids of the *iso*quinoline group which arose from the observation by Perkin and Robinson (*J.*, 1911, **99**, 775) that α-gnoscopine [(±)-narcotine; (X)] could be obtained in small yield by the condensation of cotarnine (VII; R = OMe) with meconine (VIII; R = H) in boiling alcohol. The analogous anhydrocotarninephthalide was obtained in rather better yield under similar conditions from phthalide, but a nitro-derivative was pre-

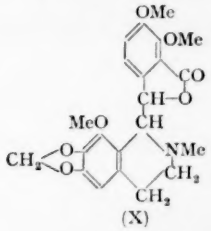
pared from 5-nitrophthalide (IX) almost quantitatively. When the nitro-group was eliminated from the product *via* the corresponding amine and hydrazine, a substance which appeared to be a stereoisomeride of anhydrocotarninephthalide was obtained. These modifications arise

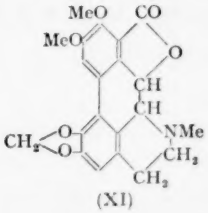

(VII)

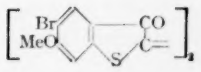

(VIII)


(IX)

from the presence of two dissimilar asymmetric carbon atoms in the structures involved (*J.*, 1911, **99**, 1153). Similarly nitromeconine (VIII; R = NO_2) gave an excellent yield of a nitro-compound from which β-gnoscopine, stereoisomeric with (±)-narcotine, was obtained (*P.*, 1910, 228; 1912, 16). The β-form, like the α-, and natural (−)-narcotine, gave cotarnine and opianic acid on oxidation with dilute nitric acid, and narceine when its methosulphate was boiled with dilute aqueous potassium hydroxide, while a partial conversion into the α-form occurred when it was heated for a long period in aqueous alcohol at 100°. Iodomeconine (VIII; R = I) and cotarnine, however, gave iodo-α-gnoscopine, which was reduced in alcoholic solution to α-gnoscopine by amalgamated aluminium (*J.*, 1914, **105**, 2085). Although Perkin and Robinson (*loc. cit.*) were able to convert α-gnoscopine into (+)- and (−)-narcotine, attempts to resolve the β-form, or one of its substitution products, were unsuccessful. Application of these synthetical reactions to hydrastinine (VII; R = H) resulted in differences in stereochemical detail (*P.*, 1912, 17; Hope, Pyman, Remfry, and Robinson, *J.*, 1931, 236). With nitromeconine the product was a mixture of two nitro-compounds subsequently reduced to the amines, which were separated. When the corresponding hydrazines were oxidised, only (±)-hydrazino-hydrastine-*a* gave a good yield of the hydrastine [(±)-hydrastine-*a*]. The other gave a little (±)-hydrastine-*b*, the main product being (±)-didehydrohydrastine, formulated as (XI). Condensation of hydrastinine with iodomeconine also gave a mixture of two substances. The relation between the synthetical bases and natural (−)-hydrastine remained obscure, but this problem was later examined in detail by Marshall, Pyman, and Robinson (*J.*, 1934, 1315). There was further work on the condensation of cotarnine with many other substances containing reactive methyl or methylene groups (*J.*, 1911, **99**, 2114; 1913, **103**, 361).


(X)


(XI)


(XII)

Perkin moved to Oxford in 1913, and the Dyson Perrins Laboratory, newly erected for him, was ready for occupation by Easter, 1916. British Dyes, Ltd., organised a team of chemists to investigate, under Perkin's direction, various problems in the manufacture of dyes and their intermediates which arose as a result of the first world war. Hope came to Oxford as a member of this team and was among the first to work in the new laboratory. At the conclusion of hostilities the chemistry school at Oxford entered upon a period of rapid expansion and development. Not only were the numbers of undergraduates very much greater than before the war, but the University had added a fourth year (the research year) to the normal chemistry course, and this was obligatory for those who wished to obtain a Class in the Final Examination. In 1919 Hope accepted an appointment as a lecturer and demonstrator in the Dyson Perrins Laboratory, and in the same year he was elected to a Fellowship at Magdalen College and became tutor in chemistry there. The change was a drastic one. After several years devoted almost entirely to research, Hope found himself confronted with heavy teaching duties, both in the laboratory and in College. He took a leading part in planning new courses of practical instruction for undergraduates and in solving the many problems which arose in the new organic chemistry department.

Although time for work at the bench was now severely restricted, Hope maintained an

active interest in research and, in conjunction with his pupils, studied several problems in the indigo group of dyes. In particular, our knowledge of the complex products which can be obtained by benzoylating indigo under various conditions was greatly extended, and structural formulæ were suggested which accounted for many of the reactions involved (*J.*, 1932, 2783; 1933, 1000; 1936, 1474). The synthesis of 5 : 5′-dibromo-6 : 6′-dimethoxy-2 : 2′-bis(oxythionaphthen) (XII) gave a product which was indistinguishable in colour from Helindone Scarlet R, obtained by the dibromination of 6 : 6′-diethoxy-2 : 2′-bisoxythionaphthen (Helindone Orange R), from which the constitution of the latter was inferred (*J.*, 1925, **127**, 990). There were also detailed studies of the products formed by the chlorination of benzoyl chloride under certain specified conditions (*J.*, 1922, **121**, 2510; 1923, **123**, 2470), and of the benzoylation of isatin 2-anil (*J.*, 1929, 1191).

With examining work of various kinds added to his teaching duties, Hope found comparatively little time for relaxation in the ten years which followed the first world war, but he enjoyed an occasional round of golf and was fond of walking and cycling in the country round Oxford whenever the opportunity arose. He was a lover of music and a regular attender at Oxford concerts. At the end of this period Hope showed signs of the ill-health which increasingly cast a cloud over the last twenty years of his life, and compelled him to restrict his activities. He found it necessary to give up his tutorial work at Magdalen in 1933, but he remained a Fellow, and, as he never married, continued to reside in the College, where he filled various offices and ultimately became Senior Fellow. He was fortunately able to continue as a University Demonstrator and Lecturer at the Dyson Perrins Laboratory until he reached the normal retiring age at the end of September 1952. He was for many years the editor of the "Chemists' Year Book."

As a tutor Hope was both popular and successful, and gained the affection and esteem of the Magdalen men who were his pupils. In the Dyson Perrins Laboratory he came into contact with a wider circle of undergraduates to whom, as a demonstrator, he was ever ready to extend a helping hand. He combined a wide experience of practical organic chemistry with a friendly and sympathetic approach, and very large numbers of Oxford chemists remain indebted to him for the encouragement and inspiration which they received from him in the laboratory.

S. G. P. Plant.

Two new WHATMAN *products!*

ASHLESS TABLETS. These *new* disc-shaped tablets, 4 cm. diam. × 9 mm. thick, require only a few seconds shaking before dispersing completely in liquids.
Price per box of 50 tablets.....5s. 3d.

ASHLESS FLOC. A dry dispersed pulp of very low ash content; can be used as a filter aid, similarly to the Ashless Tablets, or for preparation of filter pulp beds in conical or Buchner funnels. Packed in polythene film bags inside a box.
Price per box of ¼ lb net.....5s.

AVAILABLE THROUGH ALL RECOGNISED LABORATORY FURNISHERS.

MANSFIELD OIL-GAS PLANT
FOR LABORATORIES' GAS SUPPLY

Laboratories without a supply of gas should write for particulars of this Plant which produces gas in a simple manner from any cheap oil such as Solar Oil. . . . The gas produced has a calorific value of 1,350 B.T.U.'s per cubic foot, and is suitable for use with any appliance designed for use with coal gas and gives perfect oxidising and reducing flames.

MANSFIELD & SONS LTD
62 HAMILTON SQUARE, BIRKENHEAD

Annual Reports on the Progress of Chemistry for 1952

VOLUME XLIX PUBLISHED JULY 1953

Copies of this regular publication of The Chemical Society may now be ordered.

Price: Thirty shillings, post free.

THE CHEMICAL SOCIETY
BURLINGTON HOUSE · LONDON · W.1

H. K. LEWIS
BOOKS ON THE CHEMICAL AND ALLIED SCIENCES

Scientific and Technical Books. :: Large Stock of Recent Editions. :: Foreign Books not in stock obtained under Special Licence. :: Catalogues on request.

LENDING LIBRARY — Scientific and Technical
ANNUAL SUBSCRIPTION FROM 25s. PROSPECTUS FREE ON APPLICATION

THE LIBRARY CATALOGUE containing classified Index of Authors and Subjects revised to December 1949. Pp. xii + 1152. To subscribers 17s. 6d. net. To non-subscribers 35s. net., postage 1s. 3d. Supplement 1950 to 1952. To subscribers 3s. net; to non-subscribers 6s. net; postage 6d.

BI-MONTHLY LIST OF NEW BOOKS AND NEW EDITIONS ADDED TO THE LIBRARY POST FREE TO SUBSCRIBERS REGULARLY

H. K. LEWIS & Co. Ltd., 136 Gower Street, London, W.C.1
Telephone: EUSton 4282 (7 lines)

B.D.H. REAGENTS

for all responsible laboratories and for every aspect of laboratory practice

B.D.H. Organic and Inorganic Chemicals for Research and Analysis

'AnalaR' Reagents

Micro-Analytical Reagents

Organic Reagents for Delicate Analysis

Indicators

Microscopic Stains

Amino Acids

Sugars

Forensic Reagents

Prepared Reagents for Clinical and General Analysis

B.D.H. Concentrated Volumetric Solutions

THE BRITISH DRUG HOUSES LTD.
B.D.H. LABORATORY CHEMICALS GROUP
POOLE · DORSET

BDH

Rea/LC/5

PRINTED IN GREAT BRITAIN BY RICHARD CLAY AND COMPANY, LTD., BUNGAY, SUFFOLK.